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Assessment of Newly Available Health Effects Information

Review Draft

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Environmental Criteria and Assessment Office (MD-52)
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

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16. ABSTRACT

The second addendum to the *Air Quality Criteria for Particulate Matter and Sulfur Oxides* evaluates and assesses new scientific information that have emerged since 1982 and their implications for derivation of health-related criteria for particulate matter and sulfur oxides NAAQS. The literature through June 1986 has been reviewed thoroughly for information relevant to air quality criteria, although the document is not intended as a complete and detailed review of all literature pertaining to particulate matter and sulfur oxides.

Accordingly, the present addendum: (1) concisely summarizes key findings from the 1982 EPA criteria document and first addendum as they pertain to derivation of health-related criteria; and (2) provides an updated assessment of newly available information of potential importance for derivation of health criteria for both the particulate matter and sulfur oxides standards, with major emphasis on evaluation of human health studies published since 1982. Certain background information of crucial importance for understanding the assessed health effects findings is also concisely summarized. This includes information on physical and chemical properties of particulate matter, sulfur oxides, and associated aerosols and ambient monitoring techniques.

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U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

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AUTHORS AND CONTRIBUTORS

The following people served as authors or otherwise contributed to preparation of the present addendum. Names are listed in alphabetical order.

Dr. Lawrence J. Folinsbee
Environmental Monitoring and Services, Inc.
Chapel Hill, NC 27514

Dr. Lester D. Grant, Director
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

Dr. Timothy R. Gerrity
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Chapel Hill, NC 27514

Dr. Donald H. Horstman
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Chapel Hill, NC 27514

Dr. Howard Kehrl
Health Effects Research Lab
U.S. Environmental Protection Agency
Chapel Hill, NC 27514

Dr. Dennis Kotchmar
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

Dr. Fred Miller
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

Dr. L. Jack Roger
Environmental Monitoring and Services, Inc.
Chapel Hill, NC 27514

REVIEWERS

A preliminary draft version of the present addendum was circulated for review. Written or oral review comments were received from the following individuals, most of whom participated (along with the above authors and contributors) in a peer-review workshop held at EPA's Environmental Research Center in Research Triangle Park, NC on May 22-23, 1986.

Dr. Karim Ahmed
Natural Resources Defense Council
122 E. 42nd Street
New York, NY 10168

Mr. John Bachmann
Ambient Standards Branch (MD-12)
Office of Air Quality Planning and Standards
Environmental Protection Agency
Research Triangle Park, NC 27711

Dr. David Bates
Department of Medicine
St. Paul's Hospital
University of British Columbia
Vancouver, British Columbia
Canada V6Z 1Y6

*Dr. Robert Bechtel
National Jewish Center for Immunology
& Respiratory Disease
1400 Jackson Street
Denver, CO 80206

Dr. Per Camner
The Karolinska Institute
P.O. Box 60400
S-104 01 Stockholm
Sweden

Mr. Jeff Cohen
Ambient Standards Branch (MD-12)
Office of Air Quality Planning and Standards
Environmental Protection Agency
Research Triangle Park, NC 27711

Dr. Jack Hackney 213/922-7561
Room 51
Environmental Health Service
Rancho Los Amigos Hospital
7601 Imperial Highway
Downey, CA 90242

REVIEWERS (continued)

Dr. Carl Hayes
HERL (MD-55)
Environmental Protection Agency
Research Triangle Park, NC 27711

Dr. Ian Higgins
American Health Foundation
320 E. 43rd Street
New York, New York 10017

Dr. Steve Horvath
Prof. Inst. of Env. Stress
University of California
Santa Barbara, CA 93106

*Dr. Jane Koenig
Dept. of Environmental Health, SC-34
University of Washington
Seattle, WA 98195

Dr. Emmanuel Landau
American Public Health Assoc.
1015 15th Street, N.W.
Washington, DC 20005

Dr. Alan Marcus
Department of Mathematics
Washington State University
Pullman, WA 99164-2930

Dr. Bart Ostro
California Air Resources Board (IPA)
Research Division
1800 15th Street
Sacramento, CA 95812

Dr. Haluk Ozkaynak
KSG-EEPC
Harvard University
79 JFK Street
Cambridge, MA 02138

*Dr. William Pierson
Northwest Asthma & Allergy Center
4540 Sand Point Way, N.E.
Seattle, WA 98105

REVIEWERS (continued)

Mr. Larry J. Purdue
EMSL (MD-77)
Environmental Protection Agency
Research Triangle Park, NC 27711

Dr. Neil Roth
6115 Executive Blvd.
Rockville, MD 20852

Dr. Neil Schacter
Mt. Sinai Medical Center
24-30 Annenberg
1 Gustave L. Levy Place
New York, NY 10029

*Dr. Dean Sheppard
Cardiovascular Research Institute
University of California
San Francisco, CA 94143

Dr. Frank Speizer
Channing Laboratory
180 Longwood Avenue
Boston, MA 02115

Dr. John Spengler
Harvard School of Public Health
Department of Environmental Science & Physiology
665 Huntington Avenue
Boston, MA 02115

Dr. David L. Swift
Johns Hopkin University
School of Hygiene
615 N. Wolfe Street
Baltimore, MD 21205

*Written reviews only.

OBSERVER

The following member of the Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board attended the May 22-23, 1986 workshop as an observer on behalf of CASAC.

Dr. Timothy Larson
Environmental Engineering and Science Program
Dept. of Civil Engineering EX-100
University of Washington
Seattle, WA 98195

CHAPTER 1. INTRODUCTION

The United States Clean Air Act and its 1977 Amendments mandate that the U.S. Environmental Protection Agency (U.S. EPA) periodically review criteria for National Ambient Air Quality Standards (NAAQS) and revise such standards as appropriate. The most recent periodic review of the scientific bases underlying the NAAQS for particulate matter (PM) and sulfur oxides (SO_x) culminated in the 1982 publication of the EPA document *Air Quality Criteria for Particulate Matter and Sulfur Oxides* (U.S. EPA, 1982a), an associated PM staff paper (U.S. EPA, 1982b) which examined the implications of the revised criteria for the review of the PM NAAQS, an addendum to the criteria document addressing further information on health effects (U.S. EPA, 1982c), and another staff paper relating the revised scientific criteria to the review of the SO_x NAAQS (U.S. EPA 1982d). Based on the criteria document, addendum and staff papers, revised 24-hr and annual-average standards for PM have been proposed (Federal Register, 1984a) and public comments on the proposed revisions have been received both in written form and orally at public hearings (Federal Register, 1984b). Consideration of possible revision of the sulfur oxides NAAQS is still under way.

Since preparation of the above criteria document, addendum, and staff papers (U.S. EPA, 1982a, b, c, d), numerous new scientific studies or analyses have become available that may have bearing on the development of criteria for PM or SO_x and thus may notably impact proposed revisions of those standards now under consideration by EPA. In December 1985 the Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board met to discuss the PM proposals and possible implications of the newly available information. CASAC recommended that a second addendum to the 1982 Criteria Document (U.S. EPA, 1982a) be prepared to evaluate new studies and their implications for derivation of health-related criteria for the PM NAAQS. In the process of responding to CASAC's recommendations, the Agency also determined that it would be useful to examine studies that have emerged since 1982 on the health effects of sulfur oxides.

Accordingly, the present addendum (1) summarizes key findings from the 1982 EPA criteria document and first addendum (U.S. EPA, 1982a,c) as they pertain to derivation of health-related criteria, and (2) provides an updated assessment of newly available information of potential importance for derivation of health criteria for both the PM and SO_x standards, with major emphasis on evaluation of human health studies published since 1981. Certain background information of crucial importance for understanding the assessed health effects findings is also summarized. This includes information on physical and chemical properties of PM, sulfur oxides, and associated aerosols (including acid aerosols) and ambient monitoring techniques. However, new studies on associations between acid aerosols and health effects are being evaluated in a separate issue paper.

1.1 PHYSICAL AND CHEMICAL PROPERTIES OF AIRBORNE PARTICULATE MATTER AND AMBIENT AIR MEASUREMENT METHODS

As noted in the 1982 EPA criteria document (U.S. EPA, 1982a), airborne particles exist in many sizes and compositions that vary widely with changing source contributions and meteorological conditions. However, airborne particle mass tends to cluster in two principal size groups: coarse particles, generally larger than 2 to 3 micrometers (μm) in diameter; and fine particles, generally smaller than 2 to 3 μm in diameter. The dividing line between the coarse and the fine sizes is frequently given as 2.5 μm, but the distinction according to chemical composition is neither sharp nor fixed; it can depend on the contributing sources, on meteorology, and on the age of the aerosol.

Fine particle volume (or mass) distributions often exhibit two modes. Particles in the nuclei mode (which includes particles from 0.005 to 0.05 μm in diameter) form near sources by condensation of vapors produced by high temperature processes such as fossil-fuel combustion. Accumulation-mode particles (i.e., those 0.05-2.0 μm in diameter) form principally by coagulation or growth through vapor condensation of short-lived particles in the nuclei mode. Typically, 80 percent or more of the atmospheric sulfate mass occurs in the accumulation-mode. Particles in the accumulation mode normally do not grow into the coarse mode. Coarse particles include re-entrained surface dust, salt spray, and particles formed by mechanical processes such as crushing and grinding.

Primary particles are directly discharged from manmade or natural sources. Secondary particles form by atmospheric chemical and physical reactions, and most of the reactants involved are emitted as gaseous pollutants. In the air, particle growth and chemical transformation occur through gas-particle and particle-particle interactions. Gas-particle interactions include condensation of low-vapor-pressure molecules, such as sulfuric acid (H_2SO_4) and organic compounds, principally on fine particles. The only particle-particle interaction important in atmospheric processes is coagulation among fine particles.

As shown in Figure 1, fine atmospheric particles mainly include sulfates, carbonaceous material, ammonium, lead, and nitrate. Coarse particles consist mainly of oxides of silicon, aluminum, calcium, and iron, as well as calcium carbonate, sea salt, and material such as tire particles and vegetation-related particles (e.g., pollen, spores). The distributions of fine and coarse particles overlap; some chemical species found mainly in one mode may also be found in the other.

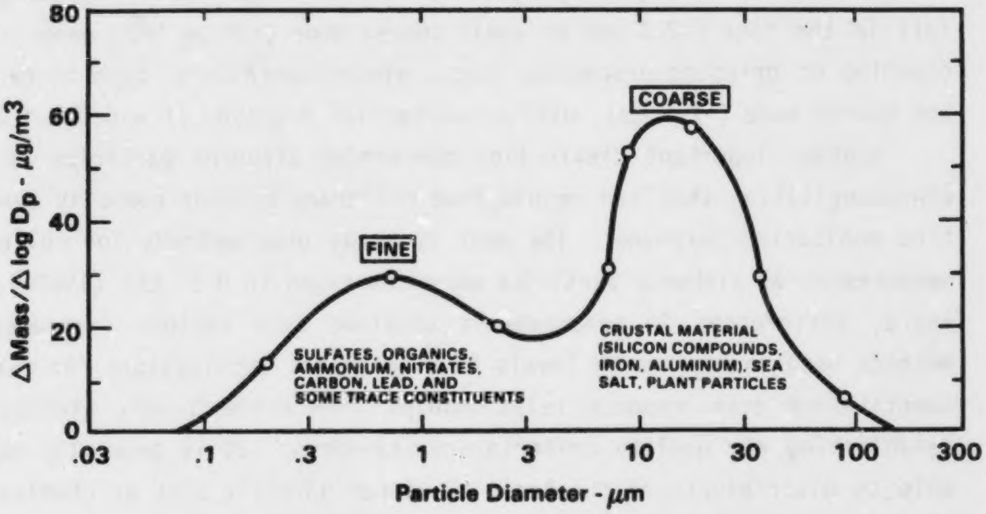

Figure 1. Representative example of typical bimodal mass distribution (measured by impactors) and chemical composition in an urban aerosol. Although some overlap exists, note substantial differences in chemical composition of fine versus coarse modes. Chemical species of each mode are listed in approximate order of relative mass contribution. Note that the ordinate is linear and not logarithmic.

Source: Modified from Whitby (1975) and NAS (1977).

The carbonaceous component of fine particles contains both elemental carbon (graphite and soot) and nonvolatile organic carbon (hydrocarbons in combustion exhaust and secondary organics formed by photochemistry). In many urban and nonurban areas, these species are the most abundant fine particles, after sulfates. Secondary organic particles form by oxidation of primary organics by a cycle that involves ozone and nitrogen oxides. Atmospheric reactions of nitrogen oxides yield nitric acid vapor (HNO_3) that may accumulate as nitrate particles in the fine or coarse modes. Most atmospheric sulfates and nitrates are water-soluble and tend to absorb moisture. Hygroscopic growth of sulfate-containing particles markedly affects their size, reactivity, and other physical properties which influence their biological and physical effects.

The relative proportions of particles of different chemical composition and size ranges can vary greatly in ambient air, depending upon emission sources from which they originate and interactions with meteorological conditions, e.g., relative humidity (RH) and temperature. Particles from combustion of fossil fuels or high-temperature processes, e.g., metal smelting, tend to fall in the fine (<2.5 μm) or small coarse mode (<10 μm MMD) range; those from crushing or grinding processes, e.g., mining operations, tend to be mainly in the coarse mode (>2.5 μm), with a substantial fraction in excess of 10 μm.

Another important distinction concerning airborne particles is the broad characterization that can result from different methods commonly used for routine monitoring purposes. The most commonly used methods for collection and measurement of airborne particles were described in U.S. EPA (1982a). As noted there, differences in measurements obtained from various instruments and methods used to measure PM levels have important implications for derivation of quantitative dose-response relationships from epidemiologic studies and for establishing air quality criteria and standards. It is generally not practicable to discriminate on the basis of either particle size or chemical composition when assessing particulate matter data from routine monitoring networks. Characteristics of the collected samples are dependent on the types of sources in the vicinity, weather conditions and sampling procedures. Difficulties that result and limitations of measurements were also discussed in detail in the 1982 EPA criteria document (U.S. EPA, 1982a).

When considering measurements of airborne particles it is essential to specify the method used and to recognize that results obtained with one method and under a given set of conditions are not necessarily applicable to other situations. For example, attempts have been made to relate findings based on smoke measurements (that relate mainly to dark-colored characteristics of particles from incomplete combustion of coal or other hydrocarbon fuels) to situations involving total suspended particulate matter (TSP) or size-specific fractions thereof (measured directly in terms of weight). Because the former (smoke) methods were used in many early epidemiological studies and the latter are now more often used for monitoring purposes in many countries, conversion from one type of measurement to the other would be desirable, but for reasons noted below, there can be no generally applicable conversion factor. Comparative evaluation of the two methods has been undertaken at numerous sites (Ball and Hume, 1977; Commins and Waller, 1967: Lee et al., 1972), but the results emphasize that they measure different qualities of the particulate matter and cannot be directly compared with one another (U.S. EPA, 1982a).

Sampling airborne particles is a complex task because of the wide spectrum of particle sizes and shapes. Separating particles by aerodynamic size provides a simplification by disregarding variations in particle shape and relying on particle settling velocity. The aerodynamic diameter of a particle is not a direct measurement of its size but is the equivalent diameter of a spherical particle of specific gravity which would settle at the same rate as the measured particles. Samplers can be designed to collect particles within sharply defined ranges of aerodynamic diameters or to simulate the deposition pattern of particles in the human respiratory system, which exhibits a more gradual transition from acceptance to exclusion of particles. High-volume (hi-vol) samplers, dichotomous samplers, cascade impactors, and cyclone samplers are the most common devices with specifically designed collection characteristics. These samplers rely on inertial impaction techniques for separating particles by aerodynamic size, filtration techniques for collecting the particles and gravimetric measurements for determining mass concentrations. Mass concentrations can also be estimated using methods that measure an integral property of particles such as optical reflectance, and empirical relationships between mass concentrations and the integral measurement can be used to predict mass concentration, if a valid physical model relating to the measurements exists and empirical data verify the model predictions.

The hi-vol sampler collects particles on a glass-fiber filter by drawing air through the filter at a flow rate of ~1.5 m^3/min, and is used to measure total suspended particulate matter (TSP). The hi-vol sampler has cutpoints of ≈25 μm at a wind speed of 24 kph and 45 μm at 2 kph. Although sampling effectiveness is wind-speed sensitive, no more than a 10 percent day-to-day variability occurs for the same ambient concentration for typical conditions. The hi-vol is one of the most reproducible particle samplers in use, with a typical coefficient of variation of 3 to 5. One major problem associated with the glass-fiber filter used on the hi-vol is formation of artifact mass caused by the presence of acid gases in the air (e.g., artifactual formation of sulfates from SO_2), which can add 6 to 7 $\mu g/m^3$ to a 24-h sample. The hi-vol has been the sampler most widely used in the U.S. for routine monitoring and has yielded TSP mass estimates used in many American epidemiological studies.

Hi-vol samplers with size-selective inlets (SSI) have recently been developed which collect and measure particles ≤10 μm or ≤15 μm. Except for the inlet, these samplers are identical in design and operation to the TSP hi-vol. Versions are now being used in epidemiologic health effects studies, and several models are being evaluated for possible routine monitoring use.

The dichotomous sampler is a low-volume gravimetric measurement device which collects fine (≤2.5 μm) and coarse (≥2.5 μm to ≤10 or 15 μm) ambient particle fractions. The sampler uses Teflon® filters which minimize artifact mass formation. The earlier inlets used with this sampler were very wind-speed dependent, but newer versions are much improved. Because of low sampling flow rate, the sampler collects submilligram quantities of particles and requires microbalance analyses, but is capable of reproducibility of ±10 percent or better. The method, however, has only begun to be employed on any major scale to generate size-selective data on PM mass assessed in relation to health effects evaluated in epidemiological studies.

Cyclone inlets with cutpoints around 2 μm have long been used to separate the fine particle fraction, can be used with samplers designed to cover a range of sampling flow rates and are available in a variety of physical sizes. Applications of cyclone inlets are found in 10- and 15-μm cutpoint inlets for both dichotomous and hi-vol samplers. Samplers with cyclone inlets could be expected to have coefficients of variations similar to those of the dichotomous or SSI hi-vol samplers, and until recently have also found only limited use in epidemiological studies of PM health effects.

Cascade impactors have been used to obtain mass distribution by particle size. Because care must be exercised to prevent errors (e.g., those due to particle bounce between stages), these samplers are normally not used as routine monitors. A study by Miller and DeKoning (1974) comparing cascade impactors with hi-vol samplers showed inconsistencies in mass collections by the impactors.

Samplers that derive mass concentrations by analytical techniques other than direct weight have been used extensively. One of the earliest was the British smokeshade (BS) sampler, which measures the reflectance of particles collected on a filter and uses empirical relationships to estimate mass concentrations. These relationships are more sensitive to carbon concentrations than mass (Bailey and Clayton, 1980) and hence are very difficult to interpret as either total or size-selective PM mass present in the atmosphere. The BS method and its standard variations typically collect PM with an ≅4.5 μm D_{50} cutpoint under field conditions, with some particles ranging from 7 to 9 μm at times being collected (McFarland et al., 1982). Thus, even if larger particles are present in the atmosphere, the BS method collects mainly fine-mode and small coarse-mode particles. The BS method neither directly measures mass nor determines chemical composition of collected PM. Rather, it measures light absorption of particles indicated by reflectance from a stain formed by particles collected on filter paper. Reflectance of light from the stain depends both on density of the stain, or amount of PM collected, and optical properties of collected PM. Smoke particles composed of elemental carbon in incomplete fossil-fuel combustion products typically make the greatest contribution to darkness of the stain, especially in urban areas. Thus, the amount of elemental carbon, but not organic carbon, in the stain tends to be most highly correlated with BS reflectance readings. Other nonblack, noncarbon particles also have optical properties which can affect the reflectance readings, but usually with negligible contribution to optical absorption.

Because the relative proportions of atmospheric carbon and noncarbon PM can vary greatly from site to site or from one time to another at the same site, the same absolute BS reflectance reading can be associated with very different amounts (or mass) of collected particles or even with very different amounts of carbon. Site-specific calibrations of reflectance readings against actual mass measurements from collocated gravimetric monitoring devices are therefore mandatory in order to obtain credible estimates of atmospheric concentrations of particulate matter based on the BS method. A single calibration curve relating mass or atmospheric concentration (in μg/m^3) of particulate matter to BS reflectance readings obtained at a given site may serve as a basis for crude estimates of the levels of PM (mainly particles <10 μm) at that site over time, so long as the chemical composition and relative proportions of elemental carbon and noncarbon PM do not change. However, the actual mass or smoke concentration at a given site may differ markedly from values calculated from a given reflectance reading on either of the two most widely used standard curves (the British and OECD standard smoke curves). Thus, much care must be taken in interpreting the meaning of any BS value reported in terms of $\mu g/m^3$, and such "nominal" expressions of airborne particle concentrations are not meaningful unless related to direct determinations of mass by gravimetric measurements carried out at the same geographical location and close in time to the BS readings.

The AISI light transmittance method is similar in approach to the BS technique, collects particles with a D_{50} cutpoint ≅5.0 μm aerodynamic diameter, uses an air intake similar to that of the BS method, and has been used for routine monitoring in some American cities. Particles are collected on a filter-paper tape periodically advanced to allow accumulation of another stain, opacity of the stain is determined by transmittance of light through the deposited material and tape, and results are expressed in terms of optical density or coefficient of haze (CoH) units per 1000 linear feet of air sampled (rather than mass units). Readings of COH units are more responsive to noncarbon particles than are BS measurements, but again, the AISI method does not directly measure mass or determine chemical composition of collected particles. Attempts to relate COH to $\mu g/m^3$ also require site-specific calibration of COH readings against mass measurements determined by a collocated gravimetric device, but the accuracy of such mass estimates are subject to question.

Since the hi-vol method collects particles much larger than those collected by BS or AISI methods, intercomparisons of PM measurements by the BS or AISI methods to equivalent TSP units, or vice versa, are very limited. For example, as shown by several studies, no consistent relationship exists between BS and TSP measurements taken at various sites or at the same site during various seasons. One exception is the relationship observed between BS and TSP during severe London air pollution episodes when low wind-speed conditions caused settling out of larger coarse-mode particles. Because fine-mode particles predominated, TSP and BS levels (in excess of ~500 $\mu g/m^3$) tended to converge, as expected if mainly fine-mode particles were present.

Many analytical techniques are available to determine chemical properties of particles collected on a suitable substrate. Most of the techniques, such as those for elemental sulfur, have been shown to be more precise than the analyses for gravimetric mass concentration. Methods are available that provide reliable analyses for sulfates, nitrates, organic fractions, and elemental composition (e.g., sulfur, lead, silicon), but not all analyses can be used for all particle samples because of factors such as incompatible substrates or inadequate sample size. Results can be misinterpreted when samples have not been appropriately segregated by particle size and when artifact mass is formed on the substrate rather than collected in particulate form, e.g., positive artifacts likely in nitrate and sulfate determinations (as noted below).

1.2 PHYSICAL/CHEMICAL PROPERTIES OF SULFUR OXIDES AND THEIR TRANSFORMATION PRODUCTS AND AMBIENT MEASUREMENT METHODS

The only sulfur oxide that occurs at significant concentrations in the atmosphere is sulfur dioxide, one of the four known gas-phase sulfur oxides (sulfur monoxide, sulfur dioxide, sulfur trioxide, and disulfur monoxide). As discussed in U.S. EPA (1982a), sulfur dioxide is a colorless gas detectable by taste at levels of 1000 to 3000 $\mu g/m^3$ (0.35-1.05 ppm). Above 10,000 $\mu g/m^3$ (3.5 ppm), it has a pungent irritating odor.

As also discussed in U.S. EPA (1982a), SO_2 is mainly removed from the atmosphere by gaseous, aqueous, and surface oxidation to form acidic sulfates. Gas-phase oxidation of SO_2 by the hydroxyl (OH) radical is well understood; not so well understood, however, is oxidation of SO_2 by hydroperoxyl (HO_2) and methyl peroxyl (CH_3O_2) radicals. The ready solubility of SO_2 in water is due mainly to formation of bisulfite (HSO_3-) and sulfite (SO_3^{2}-) ions, which are easily oxidized to form acidic sulfates by reacting with catalytic metal ions and dissolved oxidants. Sulfur dioxide reacts on the surface of a variety of airborne solid particles, such as ferric oxide, lead dioxide, aluminum oxide, salt, and charcoal.

Sulfur trioxide (SO_3), which can be emitted into the air directly or result from reactions mentioned earlier, is a highly reactive gas. In the presence of moisture in the air, it is rapidly hydrated to form sulfuric acid. In the air, then, it is sulfuric acid in the form of an aerosol that is found rather than SO_3, and it is generally associated with other pollutants in droplets or solid particles of widely varying sizes. The acid is strongly hygroscopic, and droplets containing it readily take up further moisture from the air until they are in equilibrium with their surroundings. If any ammonia is present, it reacts with sulfuric acid to form various ammonium sulfates, which continue to exist as an aerosol (in droplet or crystalline form, depending on the relative humidity).

The sulfuric acid may also react further with other compounds in the air to produce other sulfates. Some sulfates reach the air directly from combustion or industrial sources, and near oceans, sulfates exist in aerosols generated from ocean spray. As discussed in U.S. EPA (1982a), sulfate particles fall mainly in the fine-mode (<2.5 μm) size range. These particles, in the presence of moisture in air, combine with water to form coarse-mode aerosols (i.e., >2.5 μm).

Many sulfur compounds are present in the complex mixture of urban air pollutants. Some are naturally occurring and some are manmade. Total biogenic sulfur emissions in the United States have been estimated to be in the range of 5 to 6 million metric tons annually. Additional contributions from coastal and oceanic sources may also be significant. Anthropogenic (manmade) sources are estimated to emit about 26 to 27 million metric tons of SO_x (mostly SO_2) annually in the United States. Most manmade sulfur oxide emissions are from stationary point sources; over 90 percent of these are SO_2 and the rest are sulfates.

Once SO_2 is emitted into the lower atmosphere, maintenance of a tolerable environment depends on the ability of wind and turbulence to disperse the pollutants. Factors affecting the dispersion of SO_2 from combustion sources include (1) temperature and efflux velocity of the gases, (2) stack height, (3) topography and the proximity of other buildings, and (4) meteorology. Some of the SO_2 emitted into the air is removed unchanged onto various surfaces, including soil, water, grass and vegetation. The remaining SO_2 is transformed into sulfuric acid or other sulfates by various processes in the presence of moisture, and these transformation products are then removed by dry deposition processes or by precipitation. The relative proportion of SO_2 and its transformation products resulting from atmospheric processes varies with increasing distance from emission sources and residence time (age) in the atmosphere. With long-range transport (over hundreds or thousands of kilometers), extensive transformation of SO_2 to sulfates occurs, with dry deposition of acidic sulfates or their wet depositon in rain or snow contributing to acidic precipitation processes.

The most commonly used collection and measurement methods for sulfur oxides were described in the 1982 EPA criteria document (U.S. EPA, 1982a). A clear understanding of the underlying bases and limitations of particular methods is essential for adequate interpretation of epidemiological studies discussed later. If SO_2 were the only contaminant in air, all measurement methods for that gas would give comparable results, indicating the true concentration of SO_2. In typical urban environments, however, other pollutants are always present and although sampling procedures can be arranged to minimize interference from particulate matter by first filtering the air, errors still arise due to other gases and vapors. Thus, variations in specificity and accuracy of methods must be taken into account in comparing results from various studies.

Methods for measurement of SO_2 include (1) manual methods, which involve collection of the sample over a specified time period and subsequent analysis by a variety of analytical techniques, and (2) automated methods, in which sample collection and analysis are performed continuously and automatically. In the most commonly used manual methods, the analyses of the collected samples are based on colorimetric, titrimetric, turbidimetric, gravimetric, x-ray fluorescent, chemiluminescent, and ion exchange chromatographic measurement principles.

The most widely used manual method for determination of atmospheric SO_2 is the West-Gaeke pararosaniline method. An improved version of this colorimetric method, adopted in 1971 as the U.S. EPA reference method, can measure ambient SO_2 at levels as low as 25 $\mu g/m^3$ (0.01 ppm) with 30 min to 24 hr sampling time. The method has acceptable specificity for SO_2, if properly implemented; however, samples collected in tetrachloromercurate(II) can undergo temperature-dependent decay leading to the underestimation of ambient SO_2 concentrations. A variation of the method uses a buffered formaldehyde solution for sample collection, reducing the temperature-dependent decay problem. Certain American epidemiological studies employed the West-Gaeke or other variations of the pararosaniline method.

A titrimetric (acidometric) method, whereby SO_2 is collected in dilute hydrogen peroxide and the resultant H_2SO_4 is titrated with standard alkali, is the standard method mainly used in Great Britain and by the Organization for Economic Cooperation and Development (OECD). The method requires long sampling times (24 h), is subject to interference from atmospheric acids and bases, and can be affected by errors due to evaporation of reagent during sampling, titration errors, and alkaline contamination of glassware. It has been used to provide aerometric SO_2 estimates reported in many British and European epidemiological studies.

Some other methods use alkali-impregnated filter papers for collection of SO_2 and subsequent analysis as sulfite or sulfate. Most involve extraction prior to analysis; but nondispersive x-ray fluorescence allows direct measurement of SO_2 collected on sodium carbonate-impregnated membrane filters. These methods have not been widely used for routine air monitoring or epidemiological studies.

Two of the most sensitive methods for measuring SO_2 are based on chemiluminescence and ion exchange chromatography. With the former, SO_2 is absorbed in a tetrachloromercurate solution and then oxidized with potassium permanganate; oxidation of the absorbed SO_2 is accompanied by chemiluminescence detected by a photomultiplier tube. With the latter, ion exchange chromatography can be used to determine ambient levels of SO_2 absorbed into dilute hydrogen peroxide and oxidized to sulfate, or SO_2 absorbed into a buffered formaldehyde reagent. These methods have not yet been widely employed for routine monitoring uses.

Sulfation methods, based on reaction of airborne sulfur compounds with lead dioxide paste to form lead sulfate, have been used both in the United States and Europe to estimate ambient SO_2 concentrations over extended time periods. However, data obtained by sulfation methods are affected by many physical and chemical variables and other interferences (such as wind speed, temperature, and humidity); and they are not specific for SO_2, since sulfation rates are also affected by other airborne sulfur compounds (e.g., as sulfates). Thus, although sulfation rates (mg $SO_3/100\ cm^2/day$) have been converted to rough estimates of SO_2 levels (in ppm), these cannot be accepted as accurate measurements of atmospheric SO_2 levels. This is notable here because lead dioxide gauges provided estimates of SO_2 data used in some pre-1960s British epidemiological studies and also in some American epidemiologic studies.

Automated methods for measuring ambient SO_2 levels have been widely used for air monitoring. Some early continuous SO_2 analyzers, based on conductivity and coulometry, were subject to interference by many ambient air substances. More recent commercially available analyzers using these measurement principles exhibit improved specificity for SO_2 through incorporation of sophisticated chemical and physical scrubbers.

Continuous SO_2 analyzers that use flame photometric detection (FPD), fluorescence, or second-derivative spectrometry are now commercially available. The FPD method involves measurement of the band emission of excited SO_2 molecules formed from sulfur species in a hydrogen-rich flame and can exhibit high sensitivity and fast response, but must be used with selective scrubbers or coupled with gas chromatographs to achieve high specificity. Fluorescence analyzers detect characteristic fluorescence of the SO_2 molecule when irradiated by UV light, have acceptable sensitivity and response times, are insensitive to sample flow rate, and require no support gases. However, they can be affected by interference due to water vapor (quenching effects) and certain aromatic hydrocarbons and must employ ways to minimize such effects. Second-derivative spectrometry can provide highly specific measurement of SO_2 in the air, with continuous analyzers based on this principle being insensitive to sample flow rate and requiring no support gases. U.S. EPA has designated continuous analyzers based on many of the above principles (conductivity, coulometry, flame photometry, fluorescence, and second-derivative spectrometry) as equivalent methods for measurement of atmospheric SO_2.

Two main methods have been used to measure total water-soluble sulfates collected on filters along with other suspended particulate matter. With the turbidimetric method, samples are collected on sulfate-free glass fiber or other efficient filters, the sulfate is extracted and precipitated with barium chloride, and the turbidity of the suspension is measured spectrophotometrically. Samples are normally collected over 24-h periods by hi-vol sampler. However, no distinction can be made between sulfates and sulfuric acid present in the air and collected on the filters; and some material present as acid in the air may be converted to neutral sulfate on the filter during sampling. With the methylthymol blue method, samples are collected as in the turbidimetric method and the extract is reacted with barium chloride, but the barium remaining in solution is then reacted with methylthymol blue and the sulfate determined colorimetrically by measurement of uncomplexed methylthymol blue. This modification allows the procedure to be automated, but the same limitations as noted for the turbidimetric method apply, including lack of distinction between sulfates and sulfuric acid.

As for sulfuric acid, no fully satisfactory method exists for its measurement in the presence of other pollutants in the air, but some procedures exist for examining acidic properties of suspended particles or acid aerosols in general. Almost all of the strong acid content of ambient aerosols consists of sulfuric acid (H_2SO_4) and its partial atmospheric neutralization product, ammonium bisulfate (NH_4HSO_4); however, ammonium sulfate [$(NH_4)_2SO_4$], the final neutralization product, is only weakly acidic. Nitric acid (HNO_3) and hydrochloric acid (HCl) are other strong acids found in the ambient air (mainly as vapors or, when incorporated into fog droplets, as constituents of acid aerosols). Ambient air acidic aerosol concentrations can be expressed in terms of μmols H^+/m^3 or as H_2SO_4 equivalent in $\mu g/m^3$ (at 98 μg/μmol). Unfortunately, no systematic surveys of average acid aerosol concentrations in United States airsheds were available at the time the 1982 EPA criteria document (1982a) was prepared, nor is such systematic survey information available for more current acidic aerosol levels. However, Lioy and Lippmann (1985) have recently summarized some of the highest levels reported for recent years in North America, including levels in the range of 20 to 30 $\mu g/m^3$ H_2SO_4 (1 hr mean). This is in contrast to the highest level (680 $\mu g/m^3$ H_2SO_4 1 hr mean) recorded in the United Kingdom in London in 1962 and even higher levels almost certainly present during earlier London air pollution episodes.

1.3 KEY AREAS ADDRESSED IN EMERGING NEW HEALTH EFFECTS DATA

Important new health effects information has emerged in three main areas since preparation of the 1982 EPA criteria document and addendum: (1) new data which permit more definitive characterization of respiratory tract deposition patterns for inhaled particles of various size ranges, e.g., fine-mode (<2.5 μm) vs. larger coarse mode particles (>2.5 μm, <10 μm, <15 μm, etc.); (2) new reanalyses of certain key British epidemiology studies, which used BS methods for measuring PM levels, and additional new epidemiologic studies, employing other non-gravimetric or gravimetric PM measurement methods, that assess health effects associated with exposures to PM and SO_x in contemporary urban airsheds of the 1970s and 1980s; and (3) new controlled human exposure studies which more precisely define exposure-response relationships for pulmonary function decrements and respiratory symptoms due to acute SO_2 exposure.

CHAPTER 2. RESPIRATORY TRACT DEPOSITION AND FATE

2.1 RESPIRATORY TRACT DEPOSITION AND FATE OF INHALED AEROSOLS

As discussed in U.S. EPA (1982a), the respiratory system is the major route of human exposure to airborne suspensions of particles (aerosols) and gases such as SO_2. In inhalation toxicology, deposition refers to removal from inspired air of inhaled particles or gases by the respiratory tract and the initial regional pattern of these deposited materials. Clearance refers to subsequent translocation (movement of material within the lung or to other organs), transformation, and removal of deposited substances from the respiratory tract. It can also refer to removal of reaction products formed from SO_2 or particles. Retention refers to the temporal pattern of uncleared deposited particulate materials or gases and reaction products. These phenomena are complicated by interactions that occur among particles, gases such as SO_2 or endogenous ammonia, and water vapor in the airways.

Deposition patterns of inhaled aerosols and gases are affected by physical and chemical properties, e.g., aerosol particulate size distribution, density, shape, surface area, electrostatic charge, hygroscopicity or deliquescence, chemical composition, gas diffusivity and solubility, and related reactions. The geometry of the respiratory airways from nose and mouth to the lung parenchyma also influences aerosol deposition; important morphological parameters include diameters, lengths, inclinations to vertical, and branching angles of airway segments. Physiological factors that affect deposition include breathing patterns, respiratory tract airflow dynamics, and variations of relative humidity and temperature in the airways. Clearance from the respiratory tract depends on many factors, including site of deposition, chemical composition and properties of deposited particles, reaction products, mucociliary transport in the tracheobronchial tree, macrophage phagocytosis, and pulmonary lymph and blood flow. An understanding of respiratory tract anatomy and regional deposition and clearance of particles is essential for interpretation of the results of health effects studies discussed later.

The respiratory tract includes the passages of the nose, mouth, nasopharynx, oropharynx, epiglottis, larynx, trachea, bronchi, bronchioles, and small ducts and alveoli of the pulmonary acini. In regard to respiratory tract deposition and clearance of inhaled aerosols, three main regions can be considered: (1) the extrathoracic (ET) region, which includes the airways extending from the nares down to the epiglottis and larynx at the entrance to the trachea (the mouth is included in this region during mouth breathing); (2) the tracheobronchial (TB) region, which includes the primary conducting airways of the lung from the trachea to the terminal bronchioles (i.e., that portion of the lower respiratory tract having a ciliated epithelium); and (3) the pulmonary (P) region, which consists of the parenchymal airspaces of the lung, including the respiratory bronchioles, alveolar ducts, alveolar sacs, atria, and alveoli (i.e., the gas-exchange region). The extrathoracic region, as defined above, corresponds exactly to the nasopharynx, as defined by the International Commission on Radiological Protection (ICRP) Task Group on Lung Dynamics (Morrow et al., 1966). The thoracic region corresponds to that portion of the respiratory tract distal to, and including, the trachea (i.e., TB + P).

As discussed in U.S. EPA (1982a), evaluation of mechanisms by which inhaled particles ultimately affect human health requires recognition of the importance of deposition and clearance phenomena in the respiratory tract. Major regions of the respiratory tract differ markedly in structure, size, function, and sensitivity or reactivity to deposited particles. They also have different mechanisms for particle elimination or clearance.

The 1982 EPA criteria document depicted available experimental deposition data for total and regional deposition in a series of figures (i.e., Figures 11-3 to 11-9 of U.S. EPA, 1982a). Curves for alveolar deposition and estimates of tracheobronchial deposition, along with an extrapolation of the upper bound of the TB curve to the point predicted by Miller et al. (1979), are reproduced here in Figure 2. Added to the figure are the more recent data of Svartengren (1986), Heyder (1986), and Emmett et al. (1982) for deposition of particles $\geq$10 μm in aerodynamic diameter (D_{ae}) in healthy adult subjects breathing through a mouthpiece.

In the studies reported by Heyder (1986), mean inspiratory flow rates of 250 and 750 cm^3s^{-1} were used with a four-second breathing cycle, resulting in minute ventilations of 7.5 and 22.5 L min^{-1}, respectively. At the higher flow rate, TB deposition of 10 μm D_{ae} particles was 0.14; fractional deposition for

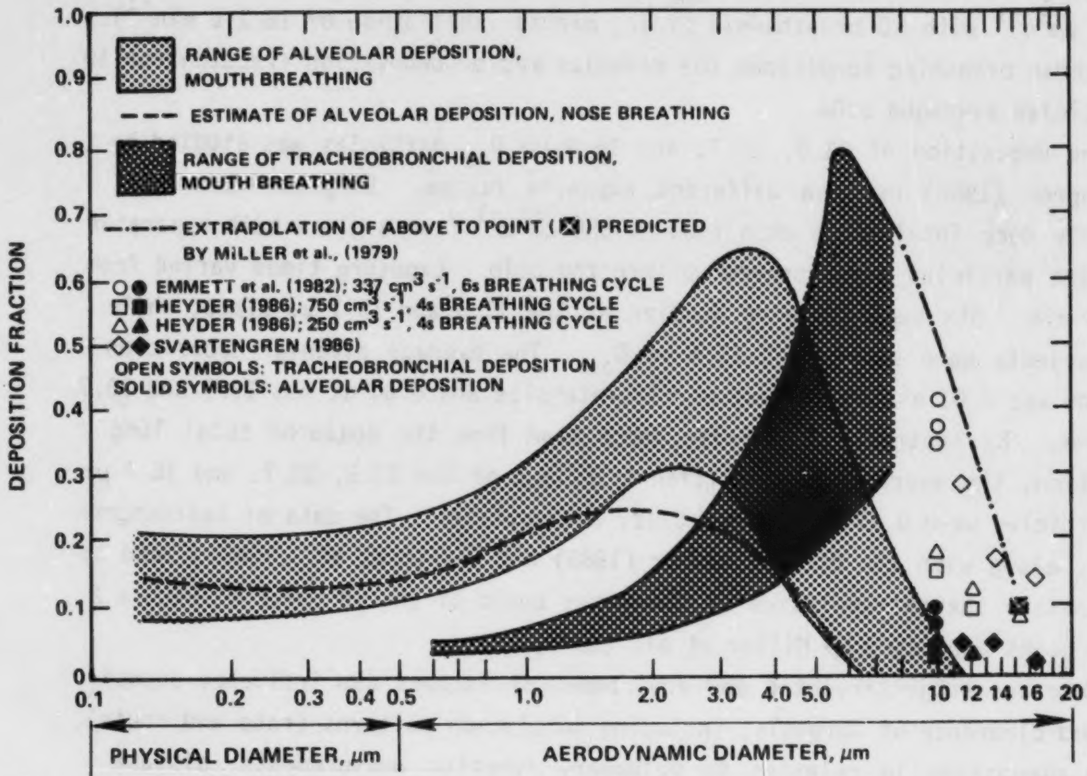

Figure 2. Regional deposition of monodisperse aerosols by indicated particle diameter for mouth breathing (alveolar, tracheobronchial) and nose breathing (alveolar). The alveolar band indicates the range of results found by different investigators using different subjects and flow parameters for alveolar deposition following mouth breathing. Variability is also expected following nasal inhalation. The tracheobronchial band indicates intersubject variability in deposition over the range of sizes as measured by Chan and Lippmann (1980). Deposition is expressed as fraction of particles entering the mouth (or nose). Also shown is an extrapolation of the upper bound of the TB curve to the point predicted by Miller et al. (1979). The extrapolation illustrates the likely shape of the curve in this size range but is uncertain. However, the data of Emmett et al. (1982), Heyder (1986), and Svartengren (1986) tend to substantiate this extrapolation. In the Svartengren (1986) studies, subjects took maximally deep inhalations at a flow of 500 $cm^3 s^{-1}$.

12 μm D_{ae} particles was 0.09. In contrast, the lower flow rate yielded deposition fractions of 0.17 and 0.12, respectively, for 10 μm and 12 μm D_{ae} particles. Emmett et al. (1982) observed an average TB deposition of 0.36 in three subjects who inhaled 10 μm D_{ae} particles at a mean inspiratory flow rate of 337 cm^3s^{-1} with 10 breaths/min (i.e., minute ventilation of 10.1 L min^{-1}). Under these breathing conditions the alveolar region deposition fraction for 10 μm particles averaged 0.06.

The deposition of 11.5, 13.7, and 16.4 μm D_{ae} particles was studied by Svartengren (1986) using a different exposure regime. Subjects took four maximally deep inhalations at a flow of 500 cm^3s^{-1} from a glass bulb apparatus each time particles were sprayed up into the bulb. Exposure times varied from 2 to 5 min. Six subjects were studied at the 11.5 and 13.7 μm sizes, while five subjects were studied at 16.4 μm D_{ae}. The average alveolar deposition fraction was 0.01 at the largest particulate size and 0.04 at the 11.5 and 13.7 μm sizes. By subtracting alveolar deposition from the measured total lung deposition, the average TB deposition fractions of the 11.5, 13.7, and 16.4 μm D_{ae} particles were 0.27, 0.17, and 0.12, respectively. The data of Svartengren (1986), along with the data of Heyder (1986) and Emmett et al. (1982), tend to substantiate the extrapolation of the upper bound of the TB curve in Figure 2 to the point predicted by Miller et al. (1979).

Numerous subject-related and environmental factors can influence deposition and clearance of aerosols, including inhalation patterns (rate and route), airway dimensions in relation to pulmonary function measurements, disease state, particle composition, and the presence of pollutant gases. Detailed discussion of effects of such factors on deposition patterns is beyond the scope of this addendum (for more details, see U.S. EPA, 1982a,b; Lippmann et al., 1980; Garrard et al., 1981; Svartengren et al., 1986; Lippmann and Schlesinger, 1984). However, the results of Heyder et al. (1982) on the biological variability of particulate deposition in controlled and spontaneous mouth breathing are of interest since this was an important issue raised in the 1982 EPA criteria document. Using both breathing patterns and particulate sizes ranging from 1 to 7μm D_{ae}, they studied total deposition and deposition rate in 20 subjects. The variability of deposition rate between subjects spontaneously breathing the same aerosol is associated with morphological and physiological factors but is mainly governed by physiological factors (i.e., primarily individual flow rate). Heyder et al. (1982) contend that this type of variability is the most important when considering health-related issues of inhaled particulate matter.

Data on respiratory tract deposition can be used to provide an evaluation of deposition of typically observed ambient particulate distributions. The similarity of experimental deposition data from human subjects breathing monodisperse aerosols in a laboratory setting to the general population breathing multimodal urban aerosols was examined in studies published after preparation of the 1982 EPA criteria document (U.S. EPA, 1982a). Hiller et al. (1982) studied total respiratory tract deposition in five subjects using a mixture of monodisperse polystyrene latex spheres 0.6, 1, and 2 μm in size. Their experimental results suggest that the deposition of mixed monodisperse and monodisperse single aerosols is similar for fine particles. However, the theoretical modeling of Diu and Yu (1983) indicate that the regional deposition patterns of polydisperse aerosols can be quite complex. They assumed a log normal size distribution and studied total and regional deposition with nasal and mouth breathing for geometric standard deviations (σ_g) of 1.0 (monodisperse), 1.5, 2.5, and 3.5. The results of Diu and Yu (1983) support the observation of Morrow (1981) that the mass deposition of mono- and polydisperse aerosols differs little if $\sigma_g < 2$. Typically, σ_g values reported for distribution of urban and rural aerosols is usually around 2 (see Chapter 5, U.S. EPA, 1982a). In the theoretical studies of Diu and Yu (1983), larger values of σ_g are predicted to impart significant complexities in regional deposition patterns due to competing mechanisms interacting with the sequential filtering effect of the respiratory tract.

Over half of the total mass of a typical ambient mass distribution would be deposited in the extrathoracic region, most of this being coarse particles, during normal nasal breathing (see Chapter 11 of U.S. EPA, 1982a). Clearance of most of this material to the esophagus would occur within minutes. Some fraction of the hygroscopic fine mass (e.g., sulfates and nitrates that grow to 2-4 μm in the respiratory tract) might also be deposited and dissolve in the extrathoracic region. Smaller fractions of both the hygroscopic and non-hygroscopic fine particles (mostly <1 μm) would be deposited in the tracheobronchial and alveolar regions, respectively. Clearance of hygroscopic material by dissolution and reaction would be relatively rapid in both regions. Clearance of insoluble coarse-mode substances would increase from less than an hour for the larger particles deposited in the upper portion of the tracheobronchial region to as much as a day for that deposited more distally. Insoluble fine and coarse particles deposited in the alveolar region have clearance half-times varying from weeks to years for the fast phase and slow phase, respectively.

With mouth-only breathing, the regional deposition pattern changes markedly, with extrathoracic deposition reduced and both tracheobronchial and pulmonary deposition enhanced. Extrathoracic deposition, although reduced, still would be dominated by coarse mode aerosols and contain little fine-mode contribution. Endogenous ammonia in human airways may, however, reduce the deposition of acid aerosols (U.S. EPA, 1982b). Remaining non-hygroscopic fine particle deposition efficiency would change little over nasal breathing (<20 percent).

In essence, regional deposition of ambient particles in the respiratory tract does not occur at divisions clearly corresponding to atmospheric aerosol distributions. Coarse-mode and hygroscopic fine-mode particles are deposited in all three regions. A fraction (5 to 25 percent) of the remaining fine-mode particles (e.g., organics and carbon not associated with hygroscopic material) is deposited in the tracheobronchial/alveolar regions. With mouth-only breathing, as illustrated in Figure 2, little particulate mass in excess of 15 μm is deposited in the thoracic region, and little mass greater than 10 μm is deposited in the alveolar region.

Oronasal breathing (partly via the mouth and partly nasally) typically occurs for healthy adults while undergoing moderate to heavy exercise. Swift and Proctor (1982) computed deposition for oronasal breathing as a function of particulate size, correcting for deposition in the parallel nasal and oral airways, and compared these results to those for mouth breathing via tube. Using minute ventilations of 24.5 and 15 $Lmin^{-1}$, their analyses predicted that total thoracic deposition at all sizes is more or less essentially the same as for pulmonary deposition noted above for mouth only breathing, i.e., with very few particles over 10 μm D_{ae} in size being likely to reach tracheobronchial regions. Tracheobronchial deposition with oronasal breathing at a higher minute ventilation (45 $Lmin^{-1}$) has been examined by Miller et al. (1984). Data for extrathoracic and tracheobronchial deposition were fit to logistic regression models yielding significantly improved fits of the deposition data. As done by Swift and Proctor (1982), a 50/50 split in airflow between the nasal and oral pathways was assumed. Simulated oronasal breathing at a minute ventilation of 45 $Lmin^{-1}$ resulted in tracheobronchial deposition fractions of 0.21, 0.17, 0.14 and 0.09 for particles of 8, 9, 10, and 12 µm in aerodynamic diameter, respectively. When the experimental deposition data of Heyder (1986), separately for nasal and oral breathing, are combined to simulate oronasal breathing, the results are in agreement with the analyses of Miller et al. (1984).

More recently, thoracic deposition and its component parts have been examined by Miller et al. (1986), as a function of particulate size, for ventilation rates ranging from normal respiration to heavy exercise in individuals who, as per Niinimaa et al. (1981), habitually breathe oronasally (mouth breathers) and in those who normally employ oronasal breathing when minute ventilations exceed about 35 $Lmin^{-1}$ (normal augmenters). Published data from various laboratories for ET and TB deposition, along with previously unpublished data of Lippmann and co-workers at New York University, were fit to logistic regression models prior to examining the influences of breathing mode and activity level on TB, P, and thoracic (TB + P) deposition. For the ET region, an impaction parameter was used that was a function of aerodynamic diameter and inspiratory flow rate, and the logistic models provided significantly improved fits of the nasal and oral inspiration data compared to the linear models of Yu et al. (1981) that also used an impaction parameter and that formed the basis of the Swift and Proctor (1982) analyses. Since TB deposition is due primarily to inertial impaction in the upper airways and to sedimentation in the lower airways, the logistic analysis for the TB region was based upon aerodynamic diameter rather than on an impaction parameter. The proportionality of airflow between the nose and mouth as a function of activity level was determined from Figure 2 of Niinimaa et al. (1981).

Thoracic deposition results given by Miller et al. (1986) are shown in Figure 3, along with the thoracic deposition results of Swift and Proctor (1982). With minute ventilations ($\dot{V}_E$) of 40 or 60 $Lmin^{-1}$ (panel A), there is not much difference between normal augmenters and mouth breathers in thoracic deposition for D_{ae} beyond the peak of the deposition curve. For $\dot{V}_E$ less than 35 $Lmin^{-1}$, the Miller et al. (1986) analyses result in substantially lower deposition in normal augmenters compared to mouth breathers. As $\dot{V}_E$ increases, thoracic deposition for normal augmenters initially decreases for a given D_{ae}, increases through the oronasal switching point, and then decreases. For mouth breathers, however, there are minimal changes in thoracic deposition at lower ventilation rates with monotonic declines in deposition as $\dot{V}_E$ increases beyond 30 $Lmin^{-1}$.

Swift and Proctor (1982) computed bands of total thoracic deposition as a fraction of particles entering the mouth and nose during oronasal and oral breathing, using $\dot{V}_E$ of approximately 24.5 $Lmin^{-1}$ and 15 $Lmin^{-1}$, respectively. The shaded area of Panel B (Figure 3) represents a composite of these data based on the lower band of the low $\dot{V}_E$ and the upper band of the higher $\dot{V}_E$. While neither Swift and Proctor (1982) nor the U.S. EPA (1982a,b) extended the bands for TB deposition beyond 8 µm, some thoracic deposition could be projected for 10 to 15 µg particles with oronasal breathing. More recent experimental data utilized in Miller et al. (1986) indicate that there is a gradual decline in thoracic deposition for large particulate sizes and that there can be significant deposition of particles greater than 10 µm, particularly for mouth breathers.

It should be noted that the deposition studies cited previously all used adult subjects, yet many of the epidemiology studies cited in the PM/SO_x criteria document (U.S. EPA, 1982a) and in this addendum report effects observed in children. Anatomical and functional differences between adults and children are likely to yield complex interactions with the major mechanisms affecting respiratory tract deposition. In a study of over 1800 Mexican-American, white, and black children 7 to 20 years of age, Hsu et al. (1979) found significant differences of lung volume and flow rate among the three races, and between male and female subjects. Further analyses of these data by Hsi et al. (1983) demonstrated that using sitting height as a predictor greatly reduced the racial differences of ventilatory function and allowed the application of a single set of prediction equations for children of all three groups. Other studies are available on normal pulmonary function values (Swiniarski et al., 1982), intrasubject variability (Hutchinson et al., 1981), influence of physical performance capacity on the growth of lung volumes (Anderson et al., 1984), and postnatal growth and size of the pulmonary acinus (Osborne et al., 1983).

To date, experimental deposition data in children's lungs are not available. Analogous to the development of mathematical models for deposition in adults, the thrust for age-dependent dosimetry modeling has been from

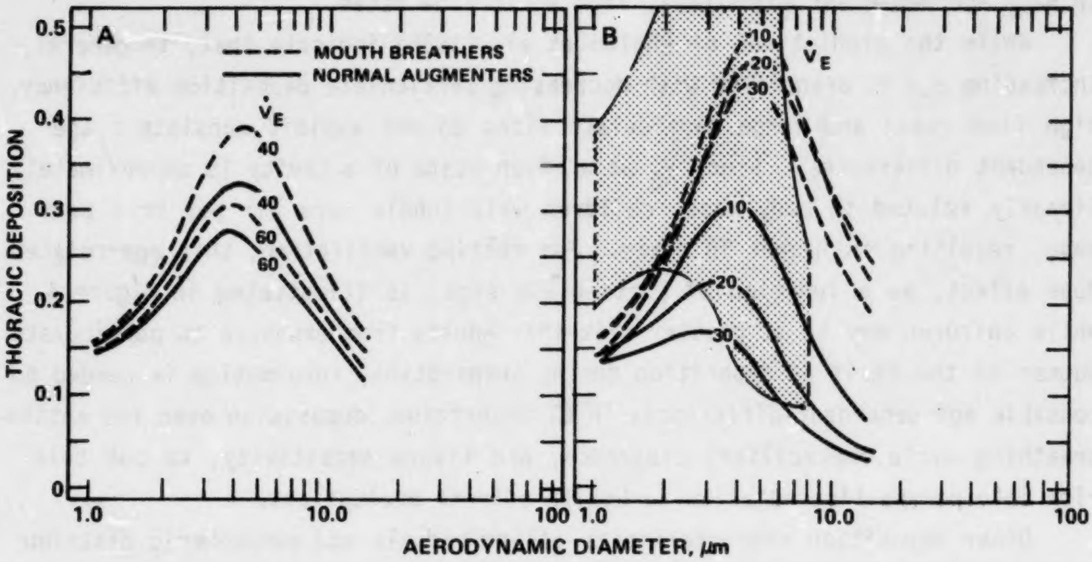

Figure 3. Estimates of thoracic deposition of particles between 1 and 15 µm by Miller et al. (1986) for normal augmenters (solid lines) and mouth breathers (broken lines) are shown for minute ventilation ($\dot{V}_E$) exceeding the switch point of 35 L min^{-1} (A) and for lower $\dot{V}_E$ (B). Normal augmenters are individuals who normally use oronasal breathing to augment respiratory airflow when $\dot{V}_E$ exceeds about 35 L min^{-1}, while mouth breather refers to those individuals who habitually breathe oronasally (Niinimaa et al., 1981). The shaded area (B) is a composite of the computed bands of thoracic deposition of particles less than 8 µm by Swift and Proctor (1982) for $\dot{V}_E$ of approximately 24.6 and 15 L min^{-1}.

scientists dealing primarily with radiological protection issues (Hofmann et al., 1979; Hofmann, 1982a,b; Crawford, 1982). More recently, Phalen et al. (1985) have studied the postnatal enlargement of human tracheobronchial airways and its implication for the deposition of particles ranging from 0.05 to 10 μm in size. They made some morphometric measurements in replica lung casts of people aged 11 days to 21 years. The model predictions for deposition during inspiration only were computed for three states of physical exertion -- low activity, light exertion, and heavy exertion. Scaling techniques were employed to make age-dependent adjustments from adult flow rates.

While the predictions of Phalen et al. (1985) indicate that, in general, increasing age is associated with decreasing particulate deposition efficiency, high flow rates and large particulate sizes do not exhibit consistent age-dependent differences. Since $\dot{V}_E$ at a given state of activity is approximately linearly related to body mass, children will inhale more air per unit body mass, resulting in higher TB doses. For resting ventilation, this age-related dose effect, as a function of particulate size, is illustrated in Figure 4. While children may be at greater risk than adults from exposure to particulate matter on the basis of deposition during inspiration, information is needed on possible age-dependent differences in ET deposition, deposition over the entire breathing cycle, mucociliary clearance, and tissue sensitivity, to put this risk into perspective relative to health effects evaluations.

Other deposition characteristics of individuals and atmospheric distributions (as well as other factors) can cause variations in regional deposition. The following examples illustrate potentially important variations in exposure/ deposition patterns:

(1) The peak in alveolar deposition efficiency for nasal and mouth-only breathing (Figure 2) tends to occur at or near the normal minimum in the bimodal distribution (2 to 4 μm MMAD). However, near emission sources or in other polluted conditions, substantial increases can occur in the coarse- or fine-mode contribution to this most efficiently deposited range.

(2) The deposition of both coarse and fine particles in the tracheobronchial region can be increased over normal ranges by increased breathing rates during exercise and by cigarette smoking, in both bronchitic and asthmatic subjects, generally reducing alveolar deposition. Since retention of particles at 24 hr was significantly lower when bronchoconstriction was induced before

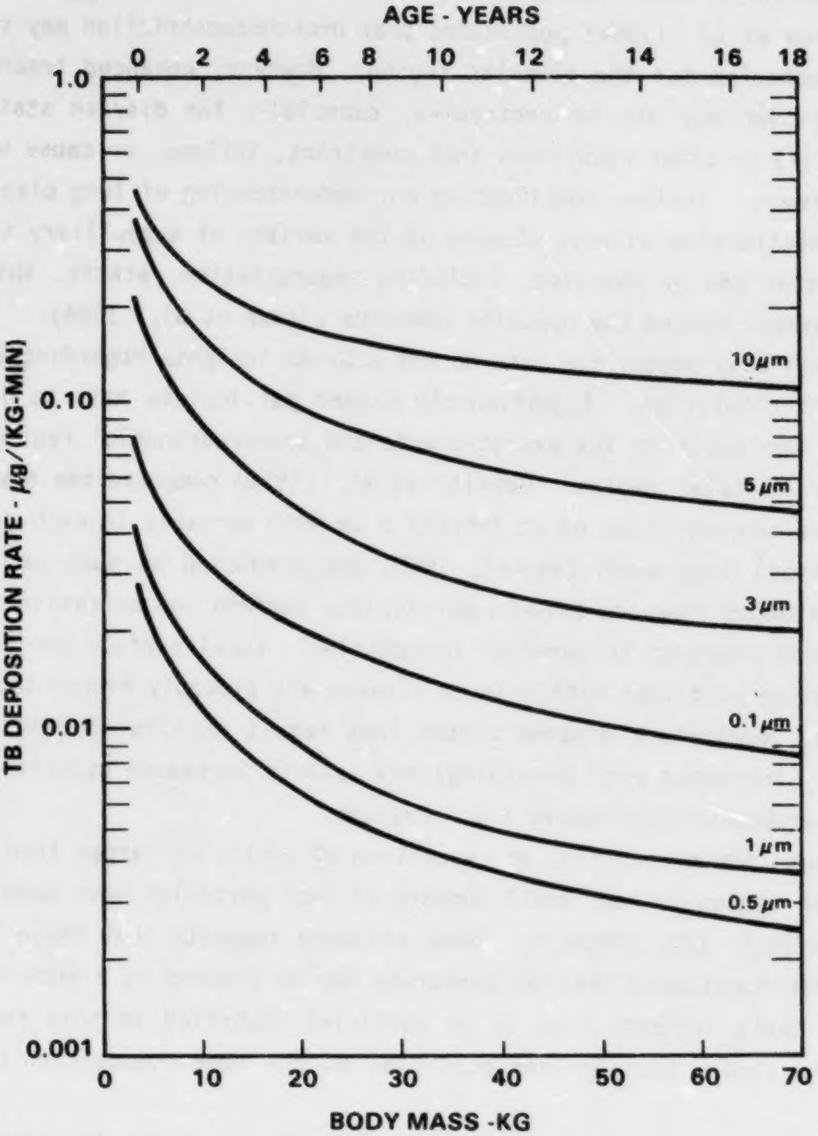

Figure 4. Predicted initial dose to the TB region as a function of body mass. Assumptions include equivalent upper airway deposition for all ages, inhalation of particles at 1 mg/m³ concentration in air, and resting minute ventilation.

Source: From Phalen et al. (1985).

inhalation of particles than when bronchoconstriction was induced after inhalation, Svartengren et al. (1984) postulated that bronchoconstriction may serve as a defense mechanism for the alveolar region. However, enhanced tracheobronchial deposition may not be protective, especially for disease states (e.g., bronchitis) or other conditions that constrict, inflame, or cause mucous build-up in airways. Further complicating our understanding of lung clearance mechanisms in obstructive airways disease is the variety of mucociliary transport patterns that can be observed, including regurgitation, stasis, spiral motion, and movement toward the opposite bronchus (Isawa et al., 1984).

(3) Regional mass deposition data do not provide insights regarding localized "hot spot" deposition. Significantly higher particulate mass to lung surface ratios can occur in the extrathoracic and tracheobronchial regions as compared to the alveolar region. Gerrity et al. (1979) computed the average particle surface concentration of an inhaled 8 μm MMAD aerosols in each generation of the Weibel lung model (Weibel, 1963) and predicted as much as two orders of magnitude difference between particulate surface concentration in the segmental bronchi compared to terminal bronchioles. Local surface concentrations of deposited particles within large airways are probably higher than the average. Also, respiratory disease states that result in altered breathing patterns (e.g., increased oral breathing) may lead to increased deposition of particles in particular respiratory tract regions.

(4) Although the probability of deposition of particles larger than 10 μm in the alveolar region is low, small numbers of such particles have been found in human lungs (U.S. EPA, 1982a,b). Some evidence suggests that those large insoluble coarse substances that do penetrate may be cleared at a much slower rate. Animal tests indicate that 15 μm particles instilled in this region clear much more slowly than smaller particles of the same composition (U.S. EPA, 1982a,b).

Besides variations in regional deposition patterns found for inhaled particles and factors affecting typical deposition patterns, regional differences exist for clearance mechanisms by which inhaled particles penetrating various levels of the respiratory tract are removed. The effects of inhaled particulate matter and other noxious agents, e.g., irritative gases, on clearance mechanisms represent one of the major categories of toxic actions exerted by such air pollutants. Detailed reviews of clearance mechanisms and effects on them due to inhaled particles and sulfur dioxide (SO_2) are presented elsewhere (U.S. EPA, 1982a,b; Lippmann et al., 1981; Lippmann and Schlesinger, 1984).

Mucociliary clearance and alveolar clearance mechanisms are of most concern here. Lung mucociliary clearance is the major defense mechanism by which inhaled particles deposited in the tracheobronchial airways are removed from the respiratory tract. Particle-laden mucus is transported by the tips of cilia which are immersed in an aqueous sol layer. Airway mucus transport rates decrease distally from the trachea (Asmundsson and Kilburn, 1970; Foster et al., 1980) with particle residence times of potentially as much as 300 minutes in the terminal bronchioles (Lee et al., 1979). Mucociliary clearance half-times of the healthy lung can range typically between 30 minutes and several hours, depending on the initial distribution of particles and mucus transport rates within each airway. Lung mucociliary clearance can be impaired by disease states of the lungs (Lippman et al., 1980). Svartengren et al. (1986) have observed marked dysfunction of lung mucociliary clearance (Camner et al., 1973; Levandowski et al., 1985; Garrard et al., 1985) and a virtual halt in tracheal mucus transport (Levandoswki et al., 1985) unless supplemented by cough. Retarded mucus transport within the lungs can lead to increased residence times of inhaled particles.

Two general types of alveolar clearance mechanisms are generally recognized: absorptive and non-absorptive. Absorptive mechanisms involve active and passive transport processes, whereby deposited particles permeate the alveolar epithelium and penetration of endothelial barriers occurs prior to uptake into the blood or lymphatic transport. These processes are most effective in removing highly soluble particles. Phagocytosis of deposited particles by alveolar macrophages is generally accepted as the chief non-absorptive clearance process. Some low-solubility materials may escape phagocytosis and accumulate as focal deposits within parenchymal tissues. In the ICRP (1979) lung model it has been suggested that as much as 40 percent of particles deposited in alveoli migrate, either free or phagocytized, to the distal portions of the ciliated airways for subsequent removal by mucociliary clearance. Alveolar clearance rates depend in large part on particle solubility. Several studies of long-term clearance of highly insoluble particles in the 1- to 4-μg range (Bailey et al., 1982; Bohning et al., 1982; Philipson et al., 1985) report two phases with half times of approximately 20 and 300 days, though Philipson et al. (1985) observed slow half-times of as much as 2500 days. Stahlhoffen et al. (1980) measured the long-term clearance of ferric oxide particles (moderately insoluble) between 1 and 9 μm MMAD and found single phase clearance half-times of between 70 and 110 days that appeared to depend on particle size.

Continuous exposures to ambient aerosols result in the simultaneous deposition and redistribution of particles. The regional dose of particles inhaled continuously may thus differ significantly from the regional pattern of acute aerosol deposition. Brain and Valberg (1974) developed a model of retention of continuously inhaled particles based on the ICRP (1966) lung model. Gerrity et al. (1983) further defined it to the Weibel (1963) lung model, taking into account individual airway mucus transport rates. The Gerrity et al. (1983) model predicts maximum doses to the trachea and respiratory bronchioles for a moderately insoluble 10-μm aerosol.

Deposition of inhaled sulfate compounds in the respiratory tract is complex and depends upon breathing patterns and physical properties of the inhaled particles. Deposition patterns and clearance mechanisms for sulfates depend upon their particular size ranges (mainly fine particles <2.5 μm) as discussed above. Of most importance is the fact that deeper penetration of particles into the respiratory tract occurs during breathing through the mouth or oronasally than during nasal breathing.

Of particular concern from a health standpoint is the fact that acidic aerosols exist in ambient air mainly in the size range of 0.3 to 0.6 μm (MMAD), well within the range of readily inhalable fine-mode particles capable of penetrating deeply into tracheobronchial and alveolar regions of the respiratory tract. Under fog conditions, where acidic components are often incorporated into water droplets of larger sizes up to 10-15 μm, concern exists in regard to the potential for health effects being associated with the increased deposition of acidic fog droplets in the tracheobronchial regions of the respiratory tract.

2.2 SULFUR DIOXIDE DEPOSITION AND CLEARANCE

As discussed in U.S. EPA (1982a,c), sulfur dioxide is soluble in water and readily absorbed upon contact with the moist surfaces of the nose and upper respiratory passages. It is well established that the gas is almost completely removed (95 to 99 percent) by nasal absorption under resting conditions in both man and laboratory animals. A recent study by Schachter and coworkers (in press) also indicates similar, almost complete, removal of SO_2 in nasal passages during nasal breathing under increased exercise conditions. Schachter et al. (in press) exposed six subjects to 2.62 mg SO_2/m^3 (1 ppm) in an environmental chamber to study nasal absorption of inhaled SO_2. A 6 min rest was followed by 4 to 6 min of exercise at 450 kpm during which subjects breathed only via the nose. A catheter was placed in the oral cavity and connected to an SO_2 analyzer. No detectable quantities of SO_2 could be measured when sampling from the mouth. In addition, saliva samples were analyzed for dissolved SO_2; no dissolved SO_2 was detected. These results confirm previous observations that the nose is extremely efficient in removing SO_2.

Other human studies indicate that SO_2 penetration to the lower respiratory tract increases with activity and increased ventilation associated with a shift from nasal to oronasal breathing at a mean $\dot{V}_E$ of 30 L min^{-1} (Niinimaa et al., 1980, 1981; D'Alfonso, 1980). Most studies on deposition of SO_2 in animals and humans have been done at concentrations greater than 2.62 mg/m^3 (1 ppm). The 95 to 99 percent removal of SO_2 by the upper respiratory tract has not been confirmed at levels ordinarily found in ambient air (generally less than 0.1 mg/m^3 [0.038 ppm]). It is expected, however, that similar deposition patterns would be observed at these lower concentrations of SO_2. Once inhaled, SO_2 is absorbed quickly into the mucus layer lining the ET and TB regions, where reactions can occur which might result in alterations in the viscosity of mucus. Absorbed SO_2 can also be transferred rapidly into the systemic circulation. Less than 15 percent of the total inhaled SO_2 is likely to be exhaled immediately, with only small amounts (about 3 percent) being desorbed during the first 15 minutes after the end of exposure (U.S. EPA, 1982a,b).

2.3 POTENTIAL MECHANISMS OF TOXICITY ASSOCIATED WITH INHALED PARTICLES AND SO_2

U.S. EPA (1982a) noted that numerous possibilities exist by which a wide variety of toxic effects may be exerted by inhaled particles once deposited in the respiratory tract. Certain general types of mechanisms of toxicity can be identified to apply across a wide range of mixtures of inhaled particles, either acting alone or in combination with other common gaseous air pollutants, such as SO_2, NO_x, or ozone. These include, for example, possible irritant effects that result in decreased air flow due to airway constriction, altered mucociliary transport and effects on alveolar macrophage activity. Other toxic effects and underlying mechanisms of action are much more chemical-specific, and depending on the particular materials involved, may include forms of systemic toxicity involving non-respiratory system organs and functions. The main focus of discussion here is on general mechanisms of toxicity rather than more chemical-specific ones.

The tracheobronchial portion of the respiratory system is the site of deposition of a mixture of fine (especially hygroscopically fine) and relatively small (<10-15 μm) coarse-mode particles. Bronchoconstriction is one common response to deposition of particles in this region and has been reported in response to short-term exposure to high levels of various "inert" dusts, as well as acid and alkaline aerosols of varying particle sizes. Bronchoconstriction produced by acute exposures is likely because of neurologically-mediated reflexive actions arising from chemical and/or mechanical stimulation of irritant neural receptors in the bronchi. Since particle deposition and epithelial nerve endings tend to concentrate near airway bifurcations, deposition at such points may exert an influence on pulmonary mechanical changes due to chemical or mechanical stimulation of receptors. Reflex coughing and bronchoconstriction due to irritant effects of particles or SO_2 on tracheobronchial region receptors may be related to effects observed in various epidemiological studies, e.g., aggravation of chronic respiratory disease states such as asthma, bronchitis, and emphysema. Also, as noted earlier, some persons with asthma or other respiratory diseases may have elevated particle deposition rates in the tracheobronchial region which may contribute to a cascading effect of further bronchoconstriction and increased particle deposition in that region.

Referring to the earlier discussion of particle clearance mechanisms, several more potential mechanisms of toxicity associated with inhalation of airborne particles can be readily discerned. This includes a plausible sequence of events by which inhaled particles can contribute to chronic obstructive pulmonary disease (Albert et al., 1973; Lippmann et al., 1980). That is, inhaled particles and noxious gases can stimulate changes in the distribution and activities of various cell types lining the tracheobronchial airways. Acute exposures to high levels of airborne particles initially stimulate increased mucus secretion and mucociliary flow useful in clearing inhaled particles.

However, with continuous or repeated exposures, more marked changes can occur, e.g., marked and persistent depression in bronchial clearance, increase in secretory cell number, increase in the thickness of the mucous layer (Lippman and Schlesinger, 1984). Also, certain particles and gases affect the number of ciliated cells or their functioning so as to alter (i.e., speed or slow) mucociliary clearance rates. Mucociliary clearance is affected by fine sulfuric acid aerosols, high levels of carbon dust, and cigarette smoke.

Because of the above mucociliary clearance phenomena, airborne particles may be importantly involved as etiological factors that contribute to various types of chronic lung diseases, as discussed by U.S. EPA (1982a,b) and Lippmann et al. (1980). This includes: likely involvement in the pathogenesis of chronic bronchitis; increasing susceptibility to acute bacterial and viral infections, especially in populations or groups (e.g., children, the elderly and cigarette smokers) already predisposed to such infections by other factors; and likely aggravation of preexisting disease states, e.g., chronic bronchitis or emphysema, or other respiratory conditions such as bronchial asthma. Also, some individuals (e.g., those with Kartagener's syndrome) have genetically inherited defects in ciliated cell function or other disease states, which result in much reduced mucociliary clearance of inhaled particles and potentially greater vulnerability to toxic effects of such particles.

Particle deposition within the alveolar region of the lungs is mainly limited to fine and coarse particles of less than 10 μm D_{ae}. Several important characteristics in the alveolar region affect responses to inhaled particles. Clearance from the alveolar region is much slower than from the tracheobronchial region. The alveolar region is the site of oxygen uptake and of various non-respiratory functions of the lungs that may be affected by pollutant exposures. Many victims of London air pollution episodes were patients suffering from cardiopulmonary diseases (e.g., emphysema and bronchitis), which normally reduce the lungs' ability to transfer oxygen to blood. Individuals with chronic lung disease and nonuniform ventilation distribution will be sensitive to pollution if only because the delivered dose to the region that is being ventilated will be higher than it would be if ventilation were normally distributed. Although this added load (due to pollution exposure) is usually tolerable in normal individuals, the added stress and chain of events may lead to fatal or irreversible damage in individuals already compromised with cardiopulmonary disease.

2.4 SUMMARY

Studies published since preparation of the earlier criteria document (U.S. EPA, 1982a) and the previous addendum (U.S. EPA, 1982c) support the conclusions reached at that time and provide clarification of several issues. In light of previously available data, new literature was reviewed with a focus towards (1) the thoracic deposition and clearance of large particles, (2) assessment of deposition during oronasal breathing, (3) deposition in possibly susceptible subpopulations, such as children, and (4) information that would relate the data to refinement or interpretation of ancillary issues, such as inter- and intrasubject variability in deposition, deposition of monodisperse versus polydisperse aerosols, etc. Major results for the first three areas are given below.

The thoracic deposition of particles ≥ 10 µm D_{ae} and their distribution in the TB and P regions was studied by a number of investigators (Svartengren, 1986; Heyder, 1986; Emmett et al., 1982). Depending upon the breathing regimen used, TB deposition ranged from 0.14 to 0.36 for 10-µm D_{ae} particles, while the range for 12-µm D_{ae} particles was 0.09 to 0.27. For particles 16.4 µm D_{ae}, a maximally deep inhalation pattern resulted in TB deposition of 0.12.

The experimental data cited above were obtained from human exposure studies in which the subjects inhaled through a mouthpiece. Some of the minute ventilations employed would more normally occur with oronasal breathing (partly via the mouth and partly nasally). Various studies (Swift and Proctor, 1982; Miller et al., 1984, 1986) have simulated deposition during oronasal breathing by adjusting for parallel nasal and oral deposition as a function of air flow through the respective compartments. While the magnitude of deposition in various regions depends heavily upon minute ventilation, there is, in general, a gradual decline in thoracic deposition for large particle sizes, and there can be significant deposition of particles greater than 10 µm D_{ae}, particularly for individuals who habitually breathe through their mouth. Thus, the deposition experiments wherein subjects inhale through a mouthpiece are relevant to examining the potential of particles to penetrate to the lower respiratory tract and pose a potentially increased risk. Increased risk may be due to increased localized dose or to the exceedingly long half-times for clearance of larger particles (Gerrity et al., 1983).

Although experimental data are not currently available for deposition of particles in the lungs of children, some trends are evident from the modeling results of Phalen et al. (1985). Phalen and co-workers made morphometric measurements in replica lung casts of people aged 11 days to 21 years and modeled deposition during inspiration as a function of activity level. They found that, in general, increasing age is associated with decreasing particulate deposition efficiency. However, very high flow rates and large particulate sizes do not exhibit consistent age-dependent differences. Since minute ventilation at a given state of activity is approximately linearly related to body mass, children receive a higher TB dose of particles than do adults and would appear to be at a greater risk, other factors (i.e., mucociliary clearance, particulate losses in the head, tissue sensitivity, etc.) being equal.

CHAPTER 3. EPIDEMIOLOGICAL STUDIES OF HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO AIRBORNE PARTICLES AND SULFUR OXIDES

Extensive published information exists concerning health effects associated with exposure to airborne particulate matter and sulfur oxides. Detailed evaluations of this extensive literature (including discussions of potential mechanisms of toxicity and findings emerging from animal toxicology experiments, controlled human exposure studies, and epidemiological studies) are provided in the 1982 EPA criteria document (U.S. EPA, 1982a), as well as several other critical reviews of the subject (WHO, 1979; Holland et al., 1979; Lippmann et al., 1980; Lippmann and Schlesinger, 1984). Key health effects findings emerging from the earlier criteria review (U.S. EPA, 1982a) are summarized below, providing a perspective against which more recently published studies are then highlighted and evaluated.

3.1. HUMAN HEALTH EFFECTS DUE TO SHORT-TERM EXPOSURES TO PARTICLES AND SULFUR OXIDES

As reviewed by U.S. EPA (1982a), much information has been generated by experimental animal studies and controlled human exposure studies in regard to health effects associated with short-term (<24 hr.) exposures to airborne particles and sulfur oxides. However, the most crucial information gained in regard to effects on human health of exposure to realistic concentrations of airborne particles has come from epidemiological studies. Complicating such studies is the frequent co-occurrence of elevated levels of sulfur oxides along with airborne particles. Attention is directed here mainly to epidemiological studies concerning the health effects of exposure to particulate matter and sulfur oxides that yield information relevant to the development of exposure-effect and exposure-response relationships.

3.1.1. Mortality Effects of Short-Term Exposures

As discussed in U.S. EPA (1982a), the most clearly defined effects on mortality arising from exposure to sulfur oxides and particulate matter have been sudden increases in the number of deaths occurring, on a day-to-day basis, during episodes of high pollution. The most notable of these occurred in the Meuse Valley in 1930, in Donora in 1948 and in London in 1952. Additional episodes with notable increases in mortality occurred in London during various winters from 1948 to 1962. Besides evaluating mortality associated with major episodes, epidemiology studies also focused on more moderate day-to-day variations in mortality within large cities in relation to PM and SO_x pollution.

The large body of literature concerning such studies carried out in the United Kingdom, elsewhere in Europe, the United States and Japan was critically reviewed in detail by U.S. EPA (1982a). As discussed there, various methodological problems with most of the studies precluded drawing of quantitative conclusions regarding exposure-effect or exposure-response relationships of importance for deriving air quality standards. Among the main problems were inadequate measurement or control for potentially confounding variables and inadequate quantitation of exposure to airborne particles, SO_2 or other associated pollutants (e.g., sulfates).

Despite such problems, U.S. EPA (1982a) concluded that the then available studies collectively indicated that mortality was clearly and substantially increased when airborne particle 24-hr concentrations exceeded 1000 $\mu g/m^3$ (as measured by the BS method) in conjunction with elevations of SO_2 levels in excess of 1000 $\mu g/m^3$ (with the elderly or others with severe preexisting cardiovascular or respiratory disease mainly being affected). As for evaluation of risks of mortality at lower exposure levels, U.S. EPA (1982a) concluded that studies conducted in London by Martin and Bradley (1960) and Martin (1964) yielded useful, credible bases by which to derive conclusions concerning quantitative exposure-effect relationships. Table 1 summarizes key conclusions drawn from these and other critical studies of mortality and morbidity effects associated with short-term (24-hr) exposures to particulate matter and SO_2, as stated earlier in the 1982 EPA criteria document (U.S. EPA 1982a).

The studies by Martin and Bradley (1960) and Martin (1964) dealt with a relatively small body of data on relationships between daily mortality in Greater London and daily variations in pollution (smoke and sulfur dioxide) during the winter of 1958-59. Aerometric data from multiple sampling sites used in their analysis can be considered reasonably representative of outdoor concentrations in the areas where people lived, although the inclusion of outer, less-densely populated areas meant that average exposure may have been underestimated. During the winter of 1958-59, Martin and Bradley (1960) reported that mortality increased on some days when smoke concentrations increased by more than 100 μg/m^3 over the previous day or when SO_2 concentrations increased by 70 μg/m^3 (0.025 ppm). Increases in daily mortality were up to about 1.2 times expected values assessed from 15-day moving averages. Thick fog (visibility less than 200 meters) was also associated with increases in mortality. The relative importance of the three factors (smoke, SO_2, fog) could not be clearly determined, but on the basis of other work, the authors considered that smoke was probably most important. When results were considered on an absolute basis (Lawther, 1963), it was concluded that increases in mortality became evident when the 24-hr mean concentrations of smoke and sulfur dioxide exceeded 750 μg/m^3 and 710 μg/m^3 (~0.25 ppm), respectively. Studies on day-to-day variations in mortality in London were continued in successive winters and coupled with the records of emergency hospital admissions. Martin (1964) showed correlations between both the daily mortality and hospital admission data and concentrations of smoke or SO_2. There was no clearly defined level (threshold) above which effects were seen, but fairly consistent increases in both mortality and hospital admissions occurred when concentrations of smoke and sulfur dioxide each exceeded a 24-hr mean of about 500 μg/m^3. Based on the above analyses and a reanalysis of the Martin and Bradley data set by Ware et al. (1981), U.S. EPA (1982a) concluded that small increases in mortality among the elderly and chronically ill may have been associated with BS and SO_2 levels in the range of 500 to 1000 μg/m^3. Much less certainty was attached to suggestions of possible slight increases in mortality at still lower BS or SO_2 concentrations, based on the Ware et al. (1981) reanalyses.

In subsequent years, because of reductions in London BS levels brought about by implementation of the British Clean Air Act and more gradual SO_2 reductions, only few occasions occurred when smoke or SO_2 levels exceeded 500 μg/m^3. Analyses of daily mortality in London in relation to variations in smoke and SO_2 levels during winters from 1958-59 to 1971-72 were reported by Mazumdar et al. (1981). These analyses are of special value in attempting to define lowest levels of exposure to particulate matter and/or SO_2 associated

TABLE 1. SUMMARY OF QUANTITATIVE CONCLUSIONS FROM EPIDEMIOLOGICAL STUDIES RELATING HEALTH EFFECTS TO ACUTE EXPOSURE TO AMBIENT AIR LEVELS OF SO_2 AND PM

Type of Study	Effects observed	24-hr average pollutant level (μg/m³)		Reference
		BS	SO_2	
Mortality	Clear increases in daily total mortality or excess mortality above a 15-day moving average among the elderly and persons with preexisting respiratory or cardiac disease during the London winter of 1958-59.	≥1000	≥1000	Martin and Bradley (1960); Martin (1964)
	Analogous increases in daily mortality in London during 1958-59 to 1971-72 winters.			Mazumdar et al. (1981)
	Some indications of likely increases in daily total mortality during the 1958-59 London winter, with greatest certainty (95% confidence) of increases occurring at BS and SO_2 levels above 750 μg/m³.	500-1000	500-1000	Martin and Bradley (1960)
	Analogous indications of increased mortality during 1958-59 to 1971-72 London winters, again with greatest certainty at BS and SO_2 levels above 750 μg/m³ but indications of small increases at BS levels <500 μg/m³ and possibly as low as 150-200 μg/m³.			Mazumdar et al. (1981)
Morbidity	Worsening of health status among a group of chronic bronchitis patients in London during winters from 1955 to 1960.	≥250-500*	≥500-600	Lawther (1958); Lawther et al. (1970)
	No detectable effects in most bronchitics; but positive associations between worsening of health status among a selected group of highly sensitive chronic bronchitis patients and London BS and SO_2 levels during 1967-68 winter.	<250*	<500	Lawther et al. (1970)

*Note that the 250-500 μg/m³ BS levels stated here may represent somewhat higher PM concentrations than those actually associated with the observed effects reported by Lawther (1970). This is due to the estimates of PM mass (in μg/m³ BS) used by Lawther being based on the D.S.I.R. calibration curve found by Waller (1964) to approximate closely a site-specific calibration curve developed by Waller in central London in 1956, but yielding somewhat higher mass estimates than another site-specific calibration developed by Waller a short distance away in 1963. However, the precise relationship between estimated BS mass values based on the D.S.I.R. curve versus the 1963 Waller curve cannot be clearly determined due to several factors, including the non-linearity of the two curves and their convergence at low BS reflectance values.

Source: U.S. EPA (1982a).

with increased mortality, because they include winters when levels of those pollutants never exceeded 500 μg/m^3. The results obtained for airborne particles (measured in terms of BS) were analyzed in relation to linear and quadratic models, which Mazumdar et al. (1981) found to provide good fits to the data examined after relevant potentially confounding variables, e.g., temperature and humidity, were taken into account statistically. U.S. EPA (1982a) concluded that both of the models suggest small increases in mortality at smoke levels below 500 μg/m^3 and, possibly, to as low as 150-250 μg/m^3.

In a publication newly available since completion of U.S. EPA (1982a), Mazumdar et al. (1982) reported further on three types of analyses of London mortality during the 1958-59 to 1971-72 winters: (1) year-by-year multiple regressions, (2) stratification using nested quartiles of one pollutant within another, and (3) multiple regression of a subset of high-pollution days. Steps were taken in each analysis to control for potentially confounding factors. Mortality and pollution variables were first divided by their winter means (indexed or percent) to adjust for year-to-year variation. Seasonal trends were adjusted for by treating each variable as a deviation (residual) from 15-day moving averages; these residuals were then corrected for weather factors by regressing separately indexed mortality, SO_2 and smoke residuals in temperature and humidity residuals of the same day, previous day and lag days up to 1 wk; and dummy variables were used to remove day-of-week effects. The corrected indexed pollution variables were then reconverted to absolute units by multiplying each value by the corresponding winter mean, but the mortality values were left in indexed form.

Mazumdar et al. (1982) reported that the year-by-year multiple regressions yielded generally much smaller coefficients for SO_2 (14 winter $\bar{x}$ = 1.17 percent mortality increase/mg/m^3 SO_2; $p > 0.10$) versus those for smoke (14 winter $\bar{x}$ = 25.09 percent/mg/m^3 smoke; $p < 0.01$). Also, the nested quartile analyses using 16 cells (i.e., 4 quartiles of smoke within 4 quartiles of SO_2 and vice versa), were reported as only partially successful, in that substantial covariation remained between the two pollutants in the highest and lowest quartiles. Visual inspection of other cells, the authors noted, nevertheless suggested a much larger smoke than SO_2 effect. Last, multiple regression analyses, using the 100 days during the 14 winters when the two pollutants were in their highest deciles (excluding 5 days during the 1962 episode), were reported as showing that mortality increases monotonically with smoke for fixed SO_2 levels but mortality only increased with SO_2 levels above 0.7 mg/m^3 for fixed smoke levels. The authors concluded that their analyses of London data for 14 winters support the conclusion that mortality was significantly positively associated with air pollution, but the mortality/pollution association was almost entirely due to smoke. They also noted possible contributions of SO_2 at sufficiently high pollutant levels (i.e., both SO_2 and smoke >0.7 mg/m^3). Results from linear and quadratic models of mortality regressed on smoke alone led the authors to state a preference for the quadratic model supplemented by a hypothesis that at low smoke levels (<0.3 mg/m^3), smoke serves as a surrogate for an unidentified variable (e.g., a highly toxic fraction of particulate emissions).

More recently, Ostro (1984) reported that new analyses of the same 1958-59 to 1971-72 London winter data indicate some risk of mortality even at smoke levels below 150 $\mu g/m^3$. Specifically, Ostro (1984) employed a variation of a standard multiple regression model to test whether the data supported the existence of a "threshold" at BS = 150 $\mu g/m^3$. Observations across the range of pollutant levels were divided into two segments, those falling below versus those above 150 $\mu g/m^3$. Regression analyses for data below 150 $\mu g/m^3$, controlling for important potentially confounding factors (e.g., temperature, humidity, etc.), indicated a statistically significant pollutant effect on mortality below the BS = 150 $\mu g/m^3$ ~~level~~. For 11 of 14 winters, the coefficients for mortality associations with BS values below 150 were statistically different from zero at $p \leq 0.10$. Additional analyses focused on the last seven winters, starting in 1965-66, during which there were no BS values above 500 $\mu g/m^3$. The mortality coefficients were significant at $p < 0.05$ for six years and at the 0.01 level in four of the years. Ostro (1984) concluded that these results are suggestive of a strong association of BS with mortality, holding temperature and humidity constant, at levels below 150 $\mu g/m^3$.

The Mazumdar et al. (1982) and Ostro (1984) analyses produced generally analogous results in relation to reported findings on PM effects: (1) each found significant positive associations between increased mortality and BS levels for most of the 14 London winters from 1958-59 to 1970-71, when the data were analyzed on a year-by-year basis; (2) the coefficients obtained for mortality associations with lower BS values were generally larger than values obtained with higher BS levels, a counterintuitive result; and (3) no clearly defined threshold for BS-mortality associations could be identified based on either set of analyses, both of which showed small but significant associations at levels below 500 μg/m^3 BS.*

No readily obvious reasons stand out as explaining the reported stronger correlations between lower BS values and mortality than associations seen at higher BS levels, although both Mazumdar et al. (1982) and Ostro (1984) tendered some possibilities (for example, the low levels of smoke in later years may have contained higher proportions of respirable particles or specific toxic materials). Still other questions can be raised in regard to these analyses; for example: (1) whether or not the effects of smoke and SO_2 can be credibly separated out, given the very high correlation (generally $\geq$0.80 or 0.90) between BS and SO_2 levels in the subject data set; (2) whether unmeasured variables, such as indoor air pollution levels, might have also covaried with outdoor BS and SO_2 concentrations and contributed to observed mortality effects; or (3) whether other unevaluated longer-term changes in demographic characteristics of the London population (age, socioeconomic levels, ethnic mix, etc.) over the 14 winters might not be such as to contribute to spurious apparent associations between mortality increases and BS or SO_2. Also, Roth et al. (1986) present findings suggesting that use of deviations of mortality from 15-day moving averages may hide the true relationship between pollution and mortality. None of these issues can be definitively resolved at this time, although it seems unlikely that long-term demographic shifts during the 14 year study period could account for significant year-by-year associations; nor is it likely that indoor air exposures would be consistent from year to year, given variations in yearly climatic conditions coupled with gradual changes in heating practices (shifts away from open hearth burning of coal in residences) that occurred during the 14 year study period.

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*Note: An unpublished analysis of the 1958-71 London winter data set by Shumway et al. (1983) also produced results indicative of risk below the 500 μg/m^3 level of smoke. These analyses used a general multiple regression model and detrending of data to correct for temperature and autocorrelation effects. The best model for predicting cardiovascular, respiratory or overall mortality used lagged temperature and logs of same day levels of SO_2 or smoke. Results were reported to indicate that pollution acts positively and instantaneously, whereas temperature acts negatively, with the strongest component a lag of two days. Also, the strongest associations, as measured by multiple coherence, occur at periods of 7-21 days, implying that pollution and temperature episodes must persist in order to influence mortality.

Regardless of the above considerations, the following conclusions appear warranted based on the earlier criteria review (U.S. EPA, 1982a) and present evaluation of newly available analyses of the London mortality experience: (1) markedly increased mortality occurred, mainly among the elderly and chronically ill, in association with BS and SO_2 concentrations above 1000 $\mu g/m^3$, especially during episodes when such pollutant elevations occurred for several consecutive days; (2) the relative contributions of BS and SO_2 cannot be clearly distinguished from those of each other, nor can the effects of other factors be clearly delineated, although it appears likely that coincident high humidity (fog) was also important (possibly in providing conditions leading to formation of H_2SO_4 or other acidic aerosols); (3) increased risk of mortality is associated with exposure to BS and SO_2 levels in the range of 500 to 1000 $\mu g/m^3$, clearly at concentrations in excess of ~700 to 750 $\mu g/m^3$; and (4) less certain evidence suggests possible slight increases in the risk of mortality at BS levels below 500 $\mu g/m^3$, with no specific threshold levels having yet been demonstrated or ruled out at lower concentrations of BS (e.g., at 150 $\mu g/m^3$) nor potential contribution of other plausibly confounding variables having yet been fully evaluated.

In another study of air pollution relationships with mortality reported since the earlier criteria review (U.S. EPA, 1982a), Mazumdar and Sussman (1983) evaluated associations between mortality events and daily particulate matter and SO_2 levels in Pittsburgh, PA. The analysis, limited to investigation of same-day events, reported a possible relationship between heart disease mortality/morbidity and same day particulate levels (measured in terms of COH), but not same-day SO_2 levels. The analyses specifically evaluated daily mortality rates during 1972-1977 for all of Allegheny County, PA in relation to daily average COH and SO_2 measurements obtained at each of three air monitoring stations: one at the center of the County within a high pollution section of Pittsburgh; another situated relatively near the first in a somewhat less polluted area; and a third in a distinctly cleaner area on the northeast edge of the County. Corrections for trend and seasonal factors were made by use of daily deviations from 15-day moving averages for air pollution, temperature and mortality variables. Multiple regression analyses revealed no statistically significant associations between mortality for all ages or heart disease mortality in relation to either SO_2 or COH when regressed on each variable alone. When SO_2 and COH were considered jointly, only the associations between total or heart disease mortality and COH measurements at the Hazelwood (high pollution area) station were significant at $p < 0.05$. These results, however, cannot be accepted as providing meaningful information on mortality-air pollution associations in the Pittsburgh area in view of: (1) inadequate characterization of county-wide air pollution levels against which to compare mortality rates for the entirety of Allegheny County, the SO_2 and COH levels at each of the three monitoring stations used not being highly correlated (mostly $r \leq 0.4$ to 0.5) with values at the other stations; (2) internal inconsistencies whereby larger coefficients were obtained for associations of mortality to COH readings at the cleaner air station on the edge of the County than the intermediate pollution station near the center of the County; and (3) the use of a large number of separate mortality regression analyses, from among which only two were significant at $p < 0.05$.

In addition to the above reanalyses of London mortality data, reanalyses of mortality data from New York City in relation to air pollution have been recently reported by Ozkaynak and Spengler (1985). These investigators carried out time-series analyses on a subset of New York City data included in a prior analysis by Schimmel (1978) which was critiqued during the earlier criteria review (U.S. EPA, 1982a). The present reanalyses by Ozkaynak and Spengler (1985) evaluated 14 years (1963-76) of daily measurements of mortality (the sum of heart, other circulatory, respiratory, and cancer mortality), COH, SO_2, and temperature. Prior to regression analysis, efforts were made to remove assumed low-frequency confounding by "filtering" each variable to remove its slow-moving components. This included not only use of residuals from 15-day moving averages, but also evaluation of sensitivity of results to other filters. Initial exploratory analyses estimated regression coefficients for COH and SO_2 after all variables were preprocessed with one of several filters (e.g., taking residuals from 7-, 15-, or 21-day moving averages and other filters that removed all cycles in the data that fell beyond indicated periods measured in days). Overall, the regression coefficients for COH ranged from 1.2 to 5.4 daily deaths per unit of COH, most being statistically significant ($p \leq 0.05$). Also, a reasonable range of variation in temperature specifications produced coefficients ranging from 1.3 to 1.8 deaths per COH unit. The risk coefficients of Schimmel (1978) were near the lower end of the range of coefficients found by Ozkynak and Spengler (1985). The latter investigators noted then that they were able to generate a fairly consistent set of estimates by performing a number of sensitivity analyses. They also correctly note that these initial estimates were subject to several technical limitations: (1) misclassification of population exposure can occur in using aerometric data from one fixed monitoring site; (2) the exposure index, COH, is imperfectly related to respirable particle mass levels; and (3) the range of exploratory models initially fit may not have been diverse enough. Consequently, an additional reanalysis was undertaken.

Specifically, more recent reanalysis of the New York City data reported by Ozkaynak and Spengler (1985) used standard time-series methods to control for covariates such as temperature and to handle the problem of autocorrelation. Their previous analysis was also extended by adding records of visibility and weather from three New York City airports, in order to examine spatial homogeneity of daily air pollution in New York City and to use visibility as a surrogate for aerosol extinction (b_{ext}) or for fine particle (FP) pollution as discussed by Ozkaynak et al. (1985). The most salient feature of the mortality data found by this reanalysis was a strong seasonal component which confounds direct regressions involving mortality, air pollution and weather variables. A simple trigonometric expression was used that removed the temperature cyclic component and rendered nonseasonal temperature nonsignificant. Another stationary autoregressive term was also used to exhaust the time-series structure of the mortality records. Consideration of lagged regressions and interactions did not improve the model's predictive ability. Time-series analyses were then performed with a linear model and in a multivariate manner in which corrections for seasonality and autocorrelation were introduced into the linear model. Preliminary estimates of excess deaths (e_i) or elasticities for the pollutant variables were thereby calculated, resulting in the following findings: (1) the time-series analysis showed SO_2 levels to be significantly correlated with mortality (e_{SO2} = 2.3 percent); (2) COH also contributed significantly to excess deaths (e_{COH} = 2.4 percent); (3) B_{ext}, a variable used as a surrogate for FP pollution was also a significant contributor to excess daily deaths ($\simeq$1.2 percent); and (4) the total estimated excess deaths attributable to air pollution was $\simeq$6.0 percent. The authors concluded that although these are interim results (they are also analyzing the data one year at a time and by each quarter), these findings: (1) indicate that during the study period ambient air pollution of a large urban area was contributing to mortality, (2) appear to corroborate results from cross-sectional mortality studies, and (3) indicate that particulate air pollution, even at current levels, could be of concern for public health. However, the authors again correctly noted limitations of their analyses which preclude full reliance on these preliminary results for risk assessment purposes: (1) the results reflect aggregate analyses of 14 years of data and more thorough analyses need to be done to take into account changing SO_2 and aerosol composition over the period (preliminary analyses indicate no differences in pollutant coefficients for 1963 to 1970 and 1971 to 1976); (2) the results are based on aerometric data from one monitoring station and visibility data from one airport (JFK); and (3) the effects of heat waves and influenza epidemics during the study period have not been considered in any detail in these preliminary analyses.

Hatzakis et al. (1986) recently published a study of short-term effects of air pollution on mortality in Athens, Greece, during 1975-82. Daily concentrations of SO_2 (acidimetric method) and smoke (standard British Method) measured by a five-station network in Athens were evaluated in relation to mortality data abstracted from the Joint Registries of Athens and 18 other contiguous towns in the Greater Athens area. The authors reported that adjusted daily mortality (estimated by subtracting the observed mortality value from an "expected" value, calculated after fitting a sinusoidal curve to the empirical mortality data) was significantly and positively related to SO_2 levels ($b = +0.0058$, $p = 0.05$), but not to smoke levels. Separate multiple regression analyses were done for SO_2 and smoke, controlling in each case for temperature, relative humidity, secular, seasonal, monthly and weekly variations in mortality as well as interactions of the above variables with season. Evaluation of a possible threshold for the SO_2-mortality effect was carried out by successively deleting from the regression model days with the highest SO_2 values. These analyses resulted in the authors suggesting that, if there is an SO_2 threshold, it must lie slightly below 150 $\mu g/m^3$ (mean daily value).

The latter result, as stated by the authors, is not consistent with results of other studies in which SO_2 mortality thresholds have been placed around the value of 300 $\mu g/m^3$ (or, more credibly, around 500 $\mu g/m^3$, as per U.S. EPA, 1982a). Nor is the failure to find significant associations between mortality and smoke consistent with other more usual published findings (although differences in chemical composition of PM in Athens and lack of calibration of smoke readings against gravimetric measurements make it difficult to compare smoke levels from Athens versus elsewhere). Other questions also arise which make it difficult to fully accept the reported findings, e.g.: (1) how representative are the aerometric data for the entire Athens metropolitan area from which the mortality data were abstracted, although the typography of the area, with Athens and adjoining towns situated in a coastal "bowl" surrounded by mountains, and high correlations (mostly $r > 0.50-0.60$) between pollutant readings from the five network stations suggest that the aerometric data may well be quite representative; (2) whether use of deviations of observed mortality data for 1975-82 from expected values derived from 1956-58 mortality data as a pre-high pollution baseline period is statistically sound; and (3) whether separate regression analyses for SO_2 and smoke alone are sufficient versus analyses with both these pollutants included.

In summary, the above newly available reanalyses of New York City data raise possibilities that, with additional work, further insights may emerge regarding mortality-air pollution relationships in a large U.S. urban area. However, the interim results reported thus far do not now permit definitive determination of their usefulness for defining exposure-effect relationships, given the above-noted types of caveats and limitations. Similarly, it is presently difficult to accept the findings of mortality associated with relatively low levels of SO_2 pollution in Athens, given questions stated above regarding representativeness of the monitoring data and the statistical soundness of using deviations of mortality from an earlier baseline relatively distant in time. Lastly, the newly reported analyses of mortality-air pollution relationships in Pittsburgh (Allegheny County, PA) utilized inadequate exposure characterization and the results contain sufficient internal inconsistencies, so that the analyses are not useful for delineating mortality relationships with either SO_2 or PM.

3.1.2. Morbidity Effects of Short-Term Exposures

As noted by WHO (1979), epidemiological studies can be useful in assessing morbidity effects associated with air pollution in different communities or in areas where changes in air pollution occurred over time. In such studies, where respiratory diseases are followed, it is necessary to control for age distribution, socioeconomic status, and other possibly confounding factors. It is also crucial that adequate characterization of exposure to air pollutants of interest be carried out, if quantitative conclusions are to be drawn regarding exposure-effect or dose-response relationships. However, very few of the available epidemiological studies on morbidity effects associated with short-term exposure to airborne particles allow for such conclusions, as evaluated by U.S. EPA (1982a).

Those reported by Lawther for London populations (see Table 1) were identified by U.S. EPA (1982a) as providing credible bases for drawing quantitative-type conclusions about morbidity effects associated with airborne particles (measured as smoke) and elevated SO_2 levels. Lawther et al. (1970) reported on studies carried out from 1954 to 1968 mainly in London, using a diary technique for self-assessment of day-to-day changes in conditions among bronchitic patients. A daily illness score was calculated from the diary data and related to BS and SO_2 levels and weather variables. Pollution data for most of the London studies were mean values from the group of sites used in the mortality/morbidity studies of Martin (1964); those aerometric measurements likely provide reasonable estimates of average exposure in areas where study subjects lived or worked. In early years of the studies, when pollution levels were generally high, well defined peaks in illness score were seen when concentrations of either BS or SO_2 exceeded 1000 $\mu g/m^3$. With later reductions in pollution, the changes in condition became less frequent and of smaller size. From the series of studies as a whole, up to 1968, it was concluded that the minimum pollution levels associated with significant changes in the condition of the patients was a 24-hr mean BS level of ~250 $\mu g/m^3$ together with a 24-hr mean SO_2 concentration of ~500 $\mu g/m^3$ (0.18 ppm). A later study reported by Waller (1971) showed that, with much reduced average levels of pollution, there was an almost complete disappearance of days with smoke levels exceeding 250 $\mu g/m^3$ and SO_2 levels over 500 $\mu g/m^3$ (0.18 ppm). As earlier, some correlation remained between changes in the conditions of the patients and daily concentrations of smoke and SO_2, but the changes were small at these levels and it was difficult to discriminate between pollution effects and those of adverse weather. Thus, as concluded by U.S. EPA (1982a), the observed effects (worsening of health status among chronic bronchitic patients) were clearly associated with BS levels of 250 to 500 $\mu g/m^3$ and, possibly, somewhat lower levels (<250 $\mu g/m^3$) for highly sensitive bronchitic patients.*

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*Note: Roth et al. (1986) have recently raised questions regarding how well the health indicator values used in the Lawther morbidity studies reflect actual health status and suggest that associations between temperature and health may be understated in this data set.

Since preparation of U.S. EPA (1982a) evaluations summarized in Table 1, additional studies have appeared concerning morbidity associated with short-term exposure to airborne particles and/or sulfur oxides. Dockery et al. (1982), for example, reported on pulmonary function evaluations carried out for school children in Steubenville, OH as part of the Harvard Six-Cities Study. Pulmonary function was evaluated immediately before and after air pollution episodes in 1978, 1979 and 1980, by relating spirometric measurements (appropriately corrected for height, etc.) to aerometric data (e.g., TSP and SO_2 levels) obtained from state air pollution monitors. Data for each individual child were evaluated. Linear decreases in forced vital capacity (FVC) with increasing TSP concentrations were found, and slopes were determined for linear relationships fitting the data for four different observation periods (fall, 1978; fall, 1979; spring, 1980; fall, 1980). The slope of FVC vs. TSP was calculated for 335 children with three or more observations during any of the four study periods. Of the 335 children examined, 194 were tested during more than one study period. On average, estimated FVC was approximately 2 percent lower following each alert, whereas forced expiratory volume in 0.75 sec ($FEV_{0.75}$) did not change during the 1978 study but was decreased by 4 percent during the 1979 alert. In the spring of 1980, similar declines were seen in FVC and $FEV_{0.75}$ values as were found following the previous alerts, but no significant declines were seen in fall, 1980, when pollutant levels were distinctly lower than for previous alerts (e.g., TSP levels did not exceed 160 $\mu g/m^3$ in fall, 1980). The largest declines in lung function were observed one to two weeks after the episodes. Fifty-nine percent of the children had slopes less than zero (i.e., decreasing FVC with increasing TSP). The median slope was -0.081 $mL/\mu g/m^3$, which is significantly less than zero ($p < 0.001$) by a Wilcoxan Signed Rank test. The median FVC vs. SO_2 slope was -0.057 $mL/\mu g/m^3$, also significantly ($p < 0.01$) less than zero, but the relationship with mean daily temperature was not significantly less than zero. Similar analyses performed with $FEV_{0.75}$ also showed the relationships (slopes) for SO_2 and TSP to be significantly less than zero.

Overall, these repeated measurements of lung function showed statistically significant but physiologically small and apparently reversible declines of FVC and $FEV_{0.75}$ levels to be associated with increases of 24-hr mean TSP levels. On days of testing for pulmonary function effects, the TSP levels ranged from 11.0 to 272 $\mu g/m^3$ and SO_2 levels ranged from 0.0 to 281 $\mu g/m^3$. However, maximum TSP levels of 312 or 422 $\mu g/m^3$ occurring in fall, 1978, 2 to 5 days prior to spirometric testing may have contributed to the observed declines in lung function for some children included in data analyses for that period. Similarly, the maximum SO_2 value of 455 $\mu g/m^3$ recorded on days immediately preceding the spirometric testing during the Fall, 1979 period may have accounted for observed declines in lung function. The investigators noted that it was not possible to separate the relative contributions of the two pollutants, nor were any thresholds for the observed pulmonary function decrements discernable within the above broad range of TSP and SO_2 levels. Nevertheless, these results appear to demonstrate that small, reversible changes in pulmonary function can occur as the consequence of increased concentrations of TSP and SO_2 somewhere in the above ranges. Whether such pulmonary function changes *per se* are adverse or can lead to other, irreversible changes or make the lung more susceptible to later insults remains to be resolved. Evaluations of such issues may need to take into account an apparent subset of "responders" within the population of children studied, who showed greater than average declines in lung function in relation to TSP or SO_2 levels. For example, the lowest quartile of slopes of FVC and $FEV_{0.75}$ versus TSP were -0.386 and -0.306 $mL/\mu g/m^3$, respectively.

In another series of studies conducted during the last few years, Ostro and co-workers evaluated relationships between air pollution indices for 84 standard metropolitan statistical areas (SMSA's) mostly of 100,000 to 600,000 people in size, and indices of acute morbidity effects, using data derived from the National Center for Health Statistics (NCHS) Health Interview Survey (HIS) of 50,000 households comprising about 120,000 people (Ostro, 1983; Hausman et al., 1984; Ostro, in press). In the most recent analyses reported, Ostro (in press) used HIS results from 1976 to 1981 together with estimates of fine particle (FP) mass. That is, for adults aged 18 to 65, days of work loss (WLDs), restricted activity days (RADs) and respiratory-related restricted activity days (RRADs) measured for a two-week period before the day of the survey were used as measures of morbidity and analyzed in relation to estimated concurrent two-week averages of FP or lagged in relation to estimated 2-wk FP averages from 2 to 4 weeks earlier. The FP estimates were produced from the empirically derived regression equations of Trijonis. These equations, as used here, incorporated screened airport data and two-week average TSP readings at population-oriented monitors, using these data taken from the metropolitan area of residence. Various potentially confounding factors (such as age, race, education, income, existence of a chronic health condition, and average two-week minimum temperature) were controlled for in the analyses. Various morbidity measures (WLDs, RADs, RRADs), for workers only or for all adults in general, were consistently found to be statistically significantly ($p < 0.01$ or < 0.05) related to lagged FP estimates (for air quality 2 to 4 weeks prior to the health interview data period), when analyzed for each of the individual years from 1976 to 1981. However, less consistent associations were found between the health endpoints and more concurrent FP estimates.

The approach employed by Ostro to estimate PM levels introduces into his analyses a number of uncertainties, e.g., those inherent in airport visibility measurements, FP/visibility relationships, and TSP monitoring limitations (most notably, use of the Trijonis equations characterizing FP relationships to visibility in northeastern U.S. areas may not be appropriate for western U.S. cities). On the other hand, use of this spatially averaged indicator over time within a specific area reduces some of these uncertainties. Additional uncertainties derive from use of the HIS data base, with the vast majority of data points being "0", representing no incidences of indicator effects being recalled in the prior two weeks. Questions therefore exist regarding the distributions assumed to underlie the health endpoint results and appropriate modeling, then, of morbidity-air pollution relationships. The overall patterns of results obtained from the reported analyses are also difficult to interpret. They may suggest that acute morbidity effects are associated with fine-mode particle exposures occurring 2-4 weeks earlier, but less so with immediately prior FP exposures. Variations in findings reported by other investigators regarding lag structures in data bases relating mortality or morbidity to PM exposures are not such as to rule out such a possibility. In any case, it is not now clear as to how the effects reported by Ostro (1986) might be used to estimate quantitative relationships between morbidity effects and more usual 24-hr or annual average direct gravimetric measures of particulate matter air pollution (e.g., TSP, PM_{10}, etc.).

Mazumdar and Sussman (1983), discussed earlier, not only studied relationships between mortality and measures of PM and SO_x pollution in Pittsburgh, PA during 1972-77, but also included evaluations of morbidity (indexed by emergency hospital admissions) in relationship to daily COH and SO_2 concentrations corrected for temperature and seasonal variations. Significant associations were reported between same-day COH values (which ranged from near 0.0 to 3.5

units) and total morbidity and heart disease morbidity for all ages (1 to 59 yr) and ≥ 60 yr age groups, but no consistent statistically significant associations between morbidity categories and same-day SO_2 levels (ranging from near 0 to 0.14 ppm) monitored at the same stations. However, these results cannot be taken as indicative of associations between increased morbidity and elevated PM or SO_2 levels in the Pittsburgh area, given limitations identified earlier in relation to the mortality analyses from the same study, i.e.: (1) inadequate characterization of air pollution concentrations representative of the entirety of Allegheny County from which the morbidity data were drawn, and (2) internal inconsistencies in the results, with various classes of morbidity variously being more strongly associated with SO_2 or COH measured at lower pollution stations than higher pollution stations.

Perry et al. (1983), followed 24 Denver asthmatic subjects from January through March, 1979, using twice daily self-obtained measurements of each subject's peak expiratory flow rates (from Mini-Wright Peak Flow Meters) and recording use of "as-needed" aerosolized bronchodilators and reports of airway obstruction symptoms characteristic of asthma. These measures of morbidity were tested for relationships to air pollutants using a random effects model. Dichotomous, virtual impactor samplers at two fixed monitoring sites provided daily measurements (in $\mu g/m^3$) of inhaled PM (total mass, sulfates, and nitrates), for coarse (2.5 to 15 μm) and fine fractions (<2.5 μm). CO, SO_2, O_3, temperature and barometric pressure were also measured. Of the environmental variables measured, only fine nitrates were significantly associated with increased symptom reports and increased bronchodilator usage. During the course of this study, however, TSP levels were uncharacteristically low. This limits interpretation of the study in relation to PM effects. Use of aerometric data from only two monitoring stations in Denver, with unknown distances in relation to places of residence for subjects matched to the proximal station, also limits the usefulness of the reported findings.

Bates and Sizto (1983, 1985) have also reported results of an ongoing correlational study relating hospital admissions in southern Ontario to air pollution levels. Data for 1974, 1976, 1977, and 1978 were discussed in the 1983 paper. The more recent 1985 analyses evaluated data up to 1982 and showed: (1) no relationship between respiratory admissions and SO_2 or COHs in the winter; (2) a complex relationship between asthma admissions and temperature in the winter; and (3) a consistent relationship between respiratory admissions (both asthma and nonasthma) in summer and sulfates and ozone, but not to summer COH levels. However, Bates and Sizto note that the data analyses are now complicated by long-term trends in respiratory disease admissions unlikely related to air pollution, but they nevertheless hypothesize that observed effects may be due to a mixture of oxidant and reducing pollutants which produce intensely irritating gases or aerosols in the summer but not in the winter. More definitive interpretation of these findings may be limited until additional results findings are reported from this long-term continuing study.

Of the newly-reported analyses of short-term PM/SO_x exposure-morbidity relationships discussed above, the Dockery et al. (1982) study provides the best-substantiated and most readily interpretable results. Those results, specifically, point toward decrements in lung function occurring in association with acute, short-term increases in PM and SO_2 air pollution. The small, reversible decrements appear to persist for 1-2 wks after episodic exposures to these pollutants across a wide range, with no clear delineation of threshold yet being evident. In some study periods effects may have been due to TSP and SO_2 levels ranging up to 422 and 455 $\mu g/m^3$, respectively. Notably larger decrements in lung function were discernable for a subset of children (responders) than for others. The precise medical significance of the observed decrements per se or any consequent long-term sequalae remain to be determined. The nature and magnitude of lung function decrements found by Dockery et al. (1982), it should be noted, are also consistent with: observations of Stebbings and Fogelman (1979) of gradual recovery in lung function of children during seven days following a high PM episode in Pittsburgh, PA (max 1-hr TSP estimated at 700 $\mu g/m^3$); and the report of Saric et al. (1981) of 5 percent average declines in $FEV_{1.0}$ being associated with high SO_2 days (89-235 $\mu g/m^3$).

3.2 EFFECTS ASSOCIATED WITH LONG-TERM EXPOSURES TO AIRBORNE PARTICLES AND SULFUR OXIDES

3.2.1. Mortality Effects of Chronic Exposures

WHO (1979) notes that, in countries having reliable systems for the collection and analysis of data on deaths, based on cause and area of residence, death rates for respiratory diseases have commonly been found to be higher in towns than in rural areas. Many factors, such as differences in smoking habits, occupation, or social conditions may be involved in these contrasts; however, in a number of countries, a general association between death rates from respiratory diseases and air pollution has been apparent for many decades. Analyses of these data have been of great value as a lead for epidemiologic studies, but the absence of information concerning other relevant variables, such as smoking, and the relatively crude nature of indices of pollution used in many of these studies make them unsuitable for the quantitative assessment of exposure-effect relationships.

The 1982 U.S. EPA criteria document (1982a) noted that certain large-scale "macroepidemiological" (or "ecologic" studies as termed by some) have attracted attention on the basis of reported demonstrations of associations between mortality and various indices of air pollution, e.g., PM or SO_x levels. For example, Lave & Seskin (1970) reanalyzed mortality data from England and Wales, and developed multiple regression equations in terms of pollution and socioeconomic indices. Their findings of positive correlations between mortality rates and pollution are of general interest but cannot contribute to the development of dose-response relationships because of inadequate exposure indices used in the analyses. The authors also examined similar data for standard metropolitan statistical areas (SMSAs) in the USA, and in a later paper (Lave and Seskin, 1972) attempted to assess relative effects of air pollution, climate, and home heating on mortality rates. Although equations were obtained relating death rates to measurements of suspended particulate matter and total sulfates (both by high-volume sampler), it is again doubtful whether these can be regarded as valid in the absence of more adequate information on smoking and because of inadequate characterization of exposure parameters.

Other studies reported in further publications (Lave and Seskin, 1977; Chappie and Lave, 1981) extended their earlier analyses. Based on such later work, analogous positive associations between mortality and air pollution variables were reported for the United States. Many criticisms similar to those indicated above for the earlier Lave and Seskin (1970) study apply here. Of crucial importance are basic difficulties associated with all of their analyses in terms of: (1) use of aerometric data without regard to quality assurance considerations, notably including use of sulfate measurements known to be of questionable accuracy due to artifact formation during air sampling; and (2) questions regarding how representative the air pollution data used in the analyses are as estimates of actual exposures of individuals included in their study groups. In some instances, for example, data from a single monitoring station were apparently used to estimate pollution exposures for study populations from surrounding large metropolitan areas.

The 1982 U.S. EPA criteria document (1982a) noted that further difficulties in discerning consistent patterns of association between mortality and air pollution variables are encountered when results of Lave and coworkers are compared with those obtained by others using analogous macroepidemiological approaches. For example, Mendelsohn and Orcutt (1979) carried out regression analyses of associations between 1970 mortality rates (for 404 county groups throughout the United States) and air pollution exposures retrospectively estimated on the basis of 1970 and 1974 annual average pollutant data from air monitoring sites in the same or nearby counties. Their results suggested fairly consistent (though variable) associations between mortality for some age groups (increasingly more positive with age) and sulfate levels but much less consistent and sometimes negative associations with TSP or other pollutants. The combined TSP-SO_4 pollution-health elasticity obtained by Mendelsohn and Orcutt (1979) is similar to that obtained in the earlier studies by Lave and coworkers, all falling in the range of 0.1 to 0.2.

Other results obtained by Thibodeau et al. (1980) in carrying out large scale cross-sectional analyses of the above type indicate that the regression coefficients for mortality relationships with air pollution variables are quite unstable. Also, Lipfert (1980) reported results from an analysis taking into account a smoking index based on state tax receipts, which he interpreted as showing sulfates to be least harmful of seven air pollutants (including SO_2 and TSP), although no adjustments for urban-rural differences in study population residences were used. This is in contrast to unpublished analyses of 1970 United States mortality data by Crocker et al. (1979), which found no significant relationships between air pollution and total mortality when taking into account retrospectively estimated nutritional variables and a smoking index. Also, results of Gerking and Schultz (1981), using the same data base, indicated a significant positive relationship between TSP and total mortality when using an OLS model similar to that of Lave and Seskin (1977) but found negative, though significant, air pollution coefficients after adding smoking, nutrition, exposure-to-cold, and medical-care variables to a two-equation model.

U.S. EPA (1982a) also noted that various criticisms of the above studies have been advanced by authors of the other respective studies, but it was not possible to ascertain which findings may be more valid than others. Thus, although many of the studies qualitatively suggested positive associations between mortality and chronic exposure to certain air pollutants in the United States, many key issues remained unresolved concerning reported associations and whether they are causal or not. Since preparation of the earlier Criteria Document (U.S. EPA, 1982a) additional ecological analyses have been reported regarding efforts to assess relationships between mortality and long-term exposure to particulate matter and other air pollutants.

Lipfert (1984) conducted a series of cross-sectional multiple regression analyses of 1969 and 1970 mortality rates for up to 112 U.S. SMSA's, using the same basic data set as Lave and Seskin (1978) for 1969 and taking into account various demographic, environmental and lifestyle variables (e.g., socioeconomic status and smoking). Also included in the Lipfert (1984) reanalysis were the following additional independent variables: diet; drinking water variables; use of residential heating fuels; migration; and SMSA growth. New dependent variables included age-specific mortality rates with their accompanying sex-specific age variables. Both linear and several nonlinear (e.g., quadratic or linear splines testing for possible threshold model specifications) were evaluated. Efforts to replicate the basic analyses of Lave and Seskin (1978) and to improve upon the fit of models using various specifications led Lipfert (1984) to conclude that: (1) differences existed between high and low pollution SMSAs unrelated to the magnitude of the air pollution variables, i.e. that there appear to be important variables missing from the specification; (2) correction of errors in the Lave-Seskin data improved the regression fit and significance of some of the coefficients; but (3) it was not possible to conclude whether SO_4 or TSP has a statistically significant effect on total mortality or whether either response is linear.

Lipfert (1984) then introduced additional variables of the type listed above into the reanalysis in hopes of improving the specification and to evaluate possible collinearity with the pollution variables. The fact that some observations were incomplete for some of the newly added variables necessitated the analysis of certain subsets of the original Lave-Seskin data set. Overall, for these reanalyses, in which regressions were extended to include new variables in stepwise fashion (but retaining the 7 Lave-Seskin variables as the first step in each case), adding new variables significantly improved the fit, but several of the original Lave-Seskin variables (including SO_4) became non-significant as the result of the additional variables. Further analyses included regressions for mortality restricted to central city areas versus SMSA-based regressions, with agreement between coefficients for sulfates being quite poor (and negative for central city regressions broken down by age groups <65 or >65 yr). Many of the additional explanatory variables in the above reanalyses (both for central city and SMSA regressions) were found to be statistically significant and were then employed in regressions using total mortality rates adjusted for age, nonwhite population, poverty and cigarette smoking. Results obtained with use of additional explanatory variables and varying model specifications were very mixed: (1) sulfate coefficients were quite unstable, ranging from near 0.0 to 0.049 (highly significant and corresponding to an elasticity of 6 percent); (2) TSP coefficients were similarly variable, with similar maximum elasticity; (3) in no case were TSP and sulfate variables significant in the same regression; and (4) when the full set of explanatory variables were used with the dummy pollution variables, the coefficients for the pollution variables became more significant. Lipfert (1984), based on these total mortality analyses, concluded that: (1) the Lave-Seskin specification is inadequate and provides misleading results; (2) using additional explanatory variables improves the fit; (3) the existence of thresholds for the air pollution variables can neither be proved nor disproved; (4) although difficult to separate SO_4 effects from TSP effects, the TSP coefficients displayed slightly more consistent behavior across all the data sets considered; and (5) effects for drinking water, ozone, and (to a lesser extent) coal and wood heat warrant further investigation.

Results obtained by Lipfert (1984) with further age- and sex-specific regression analyses for <65 yr old subjects, using all other variables as defined in the above total mortality regressions, produced similar results as for the total mortality analyses. That is, as explanatory variables are added, the pollution variables tend to lose significance and the r^2 values are considerably higher than those of Lave and Seskin (1978), even when using the same specifications. Based on the age- and sex-specific analyses: (1) sulfate was never significant for males (except for Lave-Seskin specifications) and only occasionally significant for females; and (2) TSP was more often significant for both males and females, especially with threshold specifications. Analogous sex-specific analyses for persons > 65 yr old revealed further interesting results: (1) the migration variable was the single most important variable and the age variable was negative; (2) sulfate was significant only with the Lave-Seskin specification (both sexes) or with other variables suppressed (females); and (3) TSP was never significant.

In sum, it is quite evident from the above results that the air pollution regression results for the U.S. data sets analyzed by Lipfert (1984) are extremely sensitive to variations in the inclusion/exclusion of specific observations (for central city versus SMSA's or different subsets of locations) or additional explanatory variables beyond those used in the earlier Lave and Seskin (1978) analyses. The results are also highly dependent upon the particular model specifications used, i.e. air pollution coefficients vary in strength of association with total or age-/sex-specific mortality depending upon the form of the specification and the range of explanatory variables included in the analyses. Lipfert's overall conclusion was that the sulfate regression coefficients are not to be taken seriously and, since sulfate and TSP interact with each other in these regressions, caution is warranted for TSP as well.

Ozkaynak and Speingler (1985) have also described recent results from ongoing attempts of a Harvard University group to improve upon some of the previous analyses of mortality and morbidity effects of air pollution in the United States. Ozkaynak and Speingler (1985) present principal findings from a cross-sectional analysis of the 1980 U.S. vital statistics and available air pollution data bases for sulfates, and fine, inhalable and total suspended particles. In these analyses, using multiple regression methods, the association between various particle measures and 1980 total mortality were estimated for 98 and 38 SMSA subsets by incorporating recent information on particle size relationships and a set of socioeconomic variables to control for potential confounding. Issues of model misspecification and spatial autocorrelation of the residuals were also investigated. Results from the various regression analyses indicated the importance of considering particle size, composition, and source information in modeling of PM-related health effects. In particular, particle exposure measures related to the respirable and/or toxic fraction of the aerosols, such as FP (fine particles) and sulfates were the most consistently and significantly associated with the reported (annual) cross-sectional mortality rates. On the other hand, particle mass measures that included coarse particles (e.g., TSP and IP) were often found to be non-significant predictors of total mortality.

The Ozkaynak and Spengler (1985) results noted above for analysis of 1980 U.S. mortality provide an interesting overall contrast to the findings of Lipfert (1984) for 1969-70 U.S. mortality data. In particular, whereas Lipfert found TSP coefficients to be most consistently statistically significant (although varying widely depending upon model specifications, explanatory variables included, etc.), Ozkaynak and Spengler found particle mass measures including coarse particles (TSP, IP) often to be non-significant predictors of total mortality. Also, whereas Lipfert found the sulfate coefficients to be even more unstable than the TSP associations with mortality (and questioned the credibility of the sulfate coefficients), Ozkaynak and Spengler found that particle exposure measures related to the respirable or toxic fraction of the aerosols (e.g., FP or sulfates) to be most consistently and significantly associated with annual cross-sectional mortality rates. It might be tempting to hypothesize that changes in air quality or other factors from the earlier data sets (for 1969-70) analyzed by Lipfert (1984) to the later data (for 1980) analyzed by Ozkaynak and Spengler (1985, 1986) may at least partly explain their contrasting results, but there is at present no basis by which to determine if this is the case or which set of findings may or may not most accurately characterize associations between mortality and chronic PM or SO_x exposures in the United States.

Selvin et al. (1984) also used regression analyses applied to ecologic data to study the influence of air quality in the U.S. on mortality. The analyses used 1968-72 mortality data aggregated by county (3082) or by groups of counties comprising 410 1970 Census Public Use Sample (PUS) areas (some of which may be a single heavily populated urban county, e.g. Los Angeles, or several sparsely populated rural counties grouped together). Total mortality, rather than cause-specific, rates were calculated for sex-, race, and age-specific categories and were then evaluated by regression analyses in relation to air quality values (for TSP, SO_2, and NO_2) extracted from data collected at 6625 monitoring stations during 1974-76. County level aerometric estimates were interpolated from average values at individual monitoring stations, and air pollution estimates for the 410 PUS areas were population-weighted averages of the county level value. Overall, various regression analyses (taking into account numerous control variables) for county-wide or PUS areas in all of the U.S. or broken down into regions (West, South, etc.) yielded extremely mixed results, with both positive and negative coefficients being obtained in various analyses for mortality in relation to TSP, SO_2, and NO_2. The authors: (1) concluded that their results provided no persuasive evidence for links between air quality and general mortality levels; (2) noted that their results were inconsistent with previously published work; and (3) opined that linear regression analyses applied to nationally collected ecologic data cannot be usefully employed to infer causal relationships between air quality and mortality. However, the manner in which the Selvin et al. (1984) study was conducted provides little basis for assigning any credibility to the results obtained, especially in view of: (1) use of 1974-76 air quality data to estimate retrospectively exposures against which to compare 1968-74 mortality data and; (2) use of mortality data aggregated by county or by groups of counties with highly variable relationships between air monitoring locations and the population groups from which the mortality data were drawn.

Turning from ecological or macroepidemiological studies of mortality relationships to chronic air pollution exposures in the U.S., Imai et al. (1986) have recently published analyses of associations between mortality from asthma and chronic bronchitis and air pollution variables in Yokkaichi, Japan. An industrial city on Ise Bay several hundred miles south of Tokyo, Yokkaichi's industrial base and harbor facilities were largely destroyed during World War II. They were later rebuilt to include the establishment in 1957 of a petroleum complex that contained the largest oil-fired power plant in Japan, which burned high-sulfur oil that resulted in large SO_2 emissions and consequent high SO_x concentrations in immediate residential/commercial areas around the harbor. This continued until stringent emission controls were put in place and resulted in dramatic decreases in SO_x concentrations in the highly polluted area around the harbor from 1972 to 1973 and thereafter. Mortality rates for the population in that high pollution area were compared against analogous rates (for bronchial asthma or chronic bronchitis including emphysema, determined from death certificates issued during 1963-83) for people living in less-polluted areas of Yokkaichi. Sulfur oxides levels (measured by the lead peroxide method) averaged across several monitoring sites in the polluted harbor area ranged from around 1.0 to 2.0 mg/day (annual average) during 1964-72 and then steadily declined from somewhat less than 1.0 mg/day in 1973 to less than 0.5

mg/day in 1982. This is in contrast to SO_x levels consistently below 0.3 mg/day (annual average) at 3 monitoring sites in the low pollution areas of the city throughout 1967 to 1982. Annual average levels for other pollutants (NO_2, TSP, Oxidants) monitored in the high pollution area were also consistently low, i.e. $\leq$0.02 ppm (NO_2), $\leq$0.05 mg/m^3 (TSP), and $\leq$0.05 ppm (oxidants, daily max hourly values) from 1974 to 1982. Results obtained indicated significant differences between chronic bronchitis mortality for persons $\geq$ 60 yr old in the high pollution area compared against rates for the same age group from the low-pollution control area for 1967-70 and extending into 1971-74, somewhat beyond the point where marked declines became evident in SO_x levels after control measures were implemented. Lagged correlations showed large significant associations between SO_x levels and chronic bronchitis mortality occurring $\geq$1 yr later in the high pollution area (the largest correlations were found for 4-5 yr lags). In contrast, bronchial asthma mortality became relatively higher in the polluted area during the 1967-70 period, and began to decrease thereafter in more immediate response to the improvement in air quality.

These findings, overall, are quite interesting in that they relate mortality changes in populations in circumscribed urban neighborhoods to air pollution indices obtained from monitoring sites spatially located in close proximity to the residences of the population groups for whom mortality rates were determined. Further, consistently elevated mortality for the elderly in the high-pollution area (relative to the control area) was evident across many years while the SO_x concentrations were high, but then declined following reductions in the SO_x levels, thus enhancing the likelihood of a causal relationship between sulfur-containing air pollution and mortality having been detected in the study. However, it is not possible to quantitate with any precision the relative contributions to the observed mortality increases of SO_2 versus sulfates or other sulfur agents (e.g., possibly H_2SO_4 aerosols likely formed in the moist air of the coastal city).

The 1982 EPA document (U.S. EPA, 1982a) also noted that other epidemiological studies have more specifically attempted to relate lung cancer mortality to chronic exposures to sulfur oxides, PM undifferentiated by chemical composition, or specific PM chemical species. However, the 1982 document concluded that little or no clear epidemiological evidence advanced to date substantiates hypothesized links between SO_2 or other sulfur oxides and cancer;

nor does there now exist credible epidemiological evidence linking increased cancer rates to elevations in PM as a class, i.e., undifferentiated as to chemical content.

3.2.2. Morbidity Effects of Long-Term Exposures

Impairment of pulmonary function is likely to be one of the effects of long-term exposures to air pollution, since the respiratory system includes tissues that receive the initial impact when toxic materials are inhaled. Acute and chronic changes in pulmonary function may be significant biological responses to air pollution exposure. A number of studies have been conducted in an effort to relate pulmonary function changes to the presence of air pollutants in European, Japanese, and American communities. However, few provide more than qualitative evidence relating pulmonary function changes to airborne particles. The few elevated earlier by U.S. EPA (1982a) as providing quantitative evidence for lung function effects due to long-term PM and/or SO_x exposure are summarized in Table 2.

One series of studies, reported on from the early 1960s to the mid-1970s, was conducted by Ferris, Anderson, and others (Ferris and Andersen, 1962; Kenline, 1962; Andersen et al., 1964; Ferris et al., 1967, 1971, 1976). The initial study involved comparison of three areas within a pulp-mill town (Berlin, New Hampshire). Kenline (1962) reported average 24-h SO_2 levels (estimated from sulfation rates) during a limited summer sampling period (August-September, 1960) to be only 16 ppb and average 24-h TSP levels for the two-month period to be 183 $\mu g/m^3$. In the original prevalence study (Ferris and Anderson, 1962; Anderson et al., 1964), no association was found between questionnaire-determined symptoms and lung function tests assessed in the winter and spring of 1961 in the three areas with differing pollution levels, after standardizing for cigarette smoking. The authors discuss why residence is a limited indicator for exposure (Anderson et al., 1964). The study was later extended to compare Berlin, New Hampshire, with the cleaner city of Chilliwack, British Columbia in Canada (Anderson and Ferris, 1965). Sulfation rates (lead candle method) and dustfall rates were higher in Berlin than in Chilliwack. The prevalence of chronic respiratory disease was greater in Berlin, but the authors concluded that this difference was due to interactions between age and smoking habits within the respective populations.

TABLE 2. SUMMARY OF QUANTITATIVE CONCLUSIONS FROM EPIDEMIOLOGICAL STUDIES RELATING HEALTH EFFECTS TO CHRONIC EXPOSURE TO AMBIENT AIR LEVELS OF SO_2 AND PM

Type of Study	Effects observed	24-hr average pollutant level (μg/m³)			Reference
		particulate matter			
		BS	TSP	SO_2	
Cross-sectional (4 areas)	Likely increased frequency of lower respiratory symptoms and decreased lung function in children in Sheffield, England	230-301*	-	181-275	Lunn et al. (1967)
Longitudinal and cross-sectional	Apparent improvement in lung function of adults in association with decreased PM pollution in Berlin, N.H.	-	180	**	Ferris et al. (1973, 1976)
Longitudinal and cross-sectional	Apparent lack of effects and symptoms, and no apparent decrease in lung function in adults in Berlin, N.H.		80-131	**	Ferris et al. (1973, 1976)

*Note that BS levels stated here in μg/m³ must be viewed as only crude estimates of the approximate PM (BS) mass levels associated with the observed health effects, given ambiguities regarding the use or non-use of site-specific calibrations in Sheffield to derive the reported BS levels in μg/m³.

**Note that sulfation rate methods indicated low atmospheric sulfur levels in Berlin, N.H. during the time of these studies. Crude estimation of SO_2 levels from that data suggest that <25-50 μg/m³ SO_2 levels were generally present in Berlin, N.H., and did not likely contribute to observed health effects.

Source: U.S. EPA (1982a).

The Berlin, New Hampshire, population was followed up in 1967 and again in 1973 (Ferris et al., 1971, 1976). During the period between 1961 and 1967, all measured indicators of air pollution fell, e.g., TSP from about 180 μg/m^3 in 1961 to 131 μg/m^3 in 1967. In the 1973 follow-up, sulfation rates nearly doubled from the 1967 level (0.469 to 0.901 mg SO_3/100/cm^2 day) while TSP values fell from 131 to 80 μg/m^3. Only limited SO_2 data were available (the mean of a series of 8-h samples for selected weeks). During the 1961 to 1967 period, standardized respiratory symptom rates decreased and there was an indication that lung function also improved. Between 1967 to 1973, age-sex standardized respiratory symptom rates and age-sex-height standardized pulmonary function levels were unchanged. Although some of the testing was done during the spring versus the summer in the different comparison years, Ferris and coworkers attempted to rule out likely seasonal effects by retesting some subjects in both seasons during one year and found no significant differences in test results. Given that the same set of investigators, using the same standardized procedures, conducted the symptom surveys and pulmonary function tests over the entire course of these studies, it is unlikely that the observed health endpoint improvements in the Berlin study population were due to variations in measurement procedures, but rather appear to have been associated with decreases in TSP levels from 180 to 131 μg/m^3. The relatively small changes observed and limited aerometric data available, however, argue for caution in placing much weight on these findings as quantitative indicators of effect or no-effect levels for health changes in adults associated with chronic exposures to PM measured as TSP.

The earlier criteria review (U.S. EPA, 1982a) also noted that one other American study provided potentially useful qualitative or quantitative information regarding association of morbidity effects in adults with ambient exposures to SO_2 or particulate matter. A cross-sectional study was conducted by Bouhuys (1978) in two Connecticut communities in which differences in respiratory and pulmonary function were examined in 3056 subjects (adults and children). Hosein (1977a) reported on aerometric data used in the study, which were obtained at three sites in Ansonia (urban) and four sites in Lebanon (rural) near the residences of study subjects. The TSP levels during the period of the study in Lebanon and Ansonia were 39.5 and 63.1 μg/m^3 and SO_2 levels were 10.9 and 13.5 μg/m^3, respectively. Site-to-site variations on the same day were frequently significant in Ansonia and also occurred in Lebanon. During the years 1966-72, annual average TSP levels in Ansonia ranged from 88 to 152 μg/m^3. No historical data for SO_2 or TSP in Lebanon were provided. Size fractionation (Hosein, 1977b) of a limited number of TSP samples in Ansonia showed that 81 percent of the TSP sample was 9.4 μm or less in diameter. Binder et al. (1976) obtained for 20 subjects in Ansonia one 24-hour measure of personal air pollution exposure for particles ($\leq$7 μm diameter), SO_2, and NO_2. Subjects with smokers in the home were exposed to significantly higher levels than those without such exposure. Personal exposure and outdoor exposures were also significantly different. The mean personal respiratory level was 114 μg/m^3 as compared to the outdoor TSP level of 58.4 μg/m^3.

An extended version of the MRC Questionnaire was administered via a computer data-acquisition terminal (Mitchell, 1976) between October 1972 and January 1973 in Lebanon and from mid-April through July 1973 in Ansonia. For children 7 to 14 yrs) the response rate varied from 91 to 96 percent for boys and girls. For adults (25 to 64 years) the response rate was 56 percent in Ansonia and 80 percent in Lebanon. After analysis of non-responder versus responder differences, the responders were considered to be representative of the total population, although some significant differences were noted between responders and non-responders for some symptom reporting and current smoking in some age groups.

Bouhuys (1978) found no differences between Ansonia and Lebanon for chronic bronchitis prevalence rates but did note that a history of bronchial asthma was highly significant for male residents of Lebanon (the cleaner town) as compared to Ansonia (the higher-pollution area). No differences were observed between the communities for pulmonary function tests adjusted for sex, age, height and smoking habits. However, three out of five symptoms (cough, phlegm, and plus one dyspnea) prevalences were significantly higher for adult non-smokers in Ansonia ($p < 0.001$). The mix of both positive and negative health effect results obtained in this cross-sectional study make it difficult to interpret. Although the study generally found few air pollution effects, the statistically significantly increased symptom rates raise questions as to whether some impact on health (due to prior PM exposures, for example) might have occurred. A follow-up longitudinal examination could have determined whether the effects persisted. Also, it may be that the reported effects related more to historical rather than current pollutant levels or to occupational exposures which were not examined.

The 1982 Criteria Document (U.S. EPA, 1982a) further indicated that apparent quantitative relationships between air pollution and lower respiratory tract illness in children were reported by Lunn et al. (1967). These investigators studied respiratory illness in 5- and 6-year old school children living in four areas of Sheffield, England. Air pollution concentrations showed a gradient in 1964 across four study areas for mean 24-hour smoke (BS) concentrations from 97 $\mu g/m^3$ to 301 $\mu g/m^3$. During the following year, the annual concentrations of smoke were about 20 percent lower and SO_2 about 10 percent higher, but the gradient was preserved for each pollutant. In high-pollution areas, individual 24-h mean smoke concentrations exceeded 500 $\mu g/m^3$ 30 to 45 times in 1964 and 0 to 15 times in 1965 for the lowest and highest pollution areas, respectively. Sulfur dioxide exceeded 500 $\mu g/m^3$ 11 to 32 times in 1964 and 0 to 23 times in 1965 for the lowest and highest pollution areas, respectively. Information on respiratory symptoms and illness was obtained by questionnaires completed by parents, by physical examination, and by tests of pulmonary function ($FEV_{0.75}$ and FVC). Socioeconomic factors (SES) were considered in the analyses, but parental smoking and home-heating systems were not. Although some differences in SES between areas were noted, gradients between areas existed even when the groups were divided by social class, number of children in house, and so on. Positive associations were found between air pollution concentrations and both upper and lower respiratory illness. Lower respiratory illness was 33 to 56 percent more frequent in the higher pollution areas than in the low-pollution area ($p <0.005$). Also, decrements in lung function, measured by spirometry tests, were closely associated with respiratory disease symptom rates.

In a second report, Lunn et al. (1970) gave results for 11-year-old children studied in 1963-64 that were similar to those found earlier for the younger group. Upper and lower respiratory illness occurred more frequently in children exposed to annual average 24-h mean smoke (BS) concentrations of 230 to 301 $\mu g/m^3$ and 24-h mean SO_2 levels of 181-275 $\mu g/m^3$ than in children exposed to smoke (BS) at 97 $\mu g/m^3$ and SO_2 at 123 $\mu g/m^3$. This report also provided additional information obtained in 1968 on 68 percent of the children who were 5 and 6 years old in 1963-64. By 1968, the reported BS concentrations were only about one-half those measured in 1964, SO_2 levels were about 10 to 15 percent below those of 1964, and the pollution gradient no longer existed; so the combined three higher pollution areas were compared with the single original low-pollution area. Lower respiratory illness prevalence measured as "colds going to chest" was 27.9 percent in the low-pollution area and 33.3 percent in the combined high-pollution areas, but the difference was not statistically significant ($p > 0.05$). Ventilatory function results were similar. Also, the 9-year-old children had less respiratory illness than the 11-year-old group seen previously. Becuase 11-year-old children generally have less respiratory illness than do 9-year olds, this represented an anomaly that the authors suggested may be due to improved air quality.

It should be noted that these Lunn et al. (1967, 1970) findings have been widely accepted (WHO, 1979; Holland et al., 1979; U.S. EPA, 1982a,b) as valid. On the basis of the results reported, it appears that increased frequency of lower respiratory symptoms and decreased lung function in children may occur with long-term exposures to annual BS levels in the range of 230 to 301 $\mu g/m^3$ and SO_2 levels of 181 to 275 $\mu g/m^3$. However, these must be taken only as very approximate observed-effect levels because of uncertainties associated with estimating PM mass based on BS readings. Also, it cannot now be concluded, based on the 1968 follow-up study, that no-effect levels were demonstrated for BS levels in the range of 48 to 169 $\mu g/m^3$ because of: (1) the likely insufficient power of the study to have detected small changes given the size of the population cohorts studied, and (2) the lack of site-specific calibration of the BS mass readings at the time of the later (1968) study. In summary, the one study by Lunn et al. (1967) provided the clearest evidence cited in the 1982 EPA criteria document (U.S. EPA, 1982a) for associations between both significant pulmonary function decrements and increased respiratory disease illnesses in children and chronic exposure to specific ambient air levels of PM and SO_2.

Since the earlier criteria review (U.S. EPA, 1982a), results of analyses of data from the ongoing Harvard study of outdoor air pollution and respiratory health status of children in six cities in the eastern and midwestern United States have been reported recently by Ware et al. (1986). Between 1974 and 1977, approximately 10,100 white preadolescent children were enrolled in the study during three successive annual visits to the cities. On the first visit, each child underwent a spirometric examination and a parent completed a standardized questionnaire regarding the child's health status and other important background information. Most of the children (8,380) were seen for a second evaluation one year later. Measurements of TSP, the sulfate fraction of TSP (TSO_4), and SO_2 concentrations at study-affiliated outdoor stations were combined with data from other public and private monitoring sites to create a record of TSP, TSO_4, and SO_2 levels in each of 9 air pollution regions during a one-year period preceding each evaluation, and for TSP during each child's lifetime up to the time of evaluation.

Analyzing data across all six cities, Ware et al. (1985) found that frequency of chronic cough (see Figure 5) was significantly associated ($p < 0.01$) with the average of 24-hr mean concentrations of all three air pollutants (TSP, TSO_4, SO_2) during the year preceding the health examination. Rates of bronchitis and a composite measure of lower respiratory illness were significantly ($p < 0.05$) associated with annual average particulate concentrations, as well as being related to measures of lifetime TSP concentrations. However, within the individual cities, temporal and spatial variation in air pollutant levels and symptom or illness rates were not significantly associated. The history of early childhood respiratory illness for lifetime residents was significantly associated with average TSP levels during the first two postnatal years within cities, but not between cities. Furthermore, pulmonary function parameters (FVC and FEV_1) were not associated with pollutant concentrations during the year immediately preceding the spirometry test (see Figure 6) or, for lifetime residents, with lifetime average concentrations, although Ferris et al. (1986) reported a small effect on lower airway function (MMEF) related to FP concentrations.

Overall, these results appear to suggest that risk may be increased for bronchitis and some other respiratory disorders in preadolescent children at moderately elevated TSP, TSO_4 and SO_2, concentrations, which do not appear to be consistently associated with pulmonary function decrements. However, the lack of consistent significant associations between morbidity endpoints and air pollution variables within individual cities argues for caution in interpreting the present results. For example, it might be argued that the non-significant associations within cities but significant symptom increases in relation to air pollutant gradients across the cities may reflect spurious correlations across the cities. On the other hand, the within city variation in air pollutant gradients and/or size of study populations within particular cities may not be sufficiently large to detect associations between the health endpoints and air pollutant variables included in the analyses. Also, the PM indices employed in

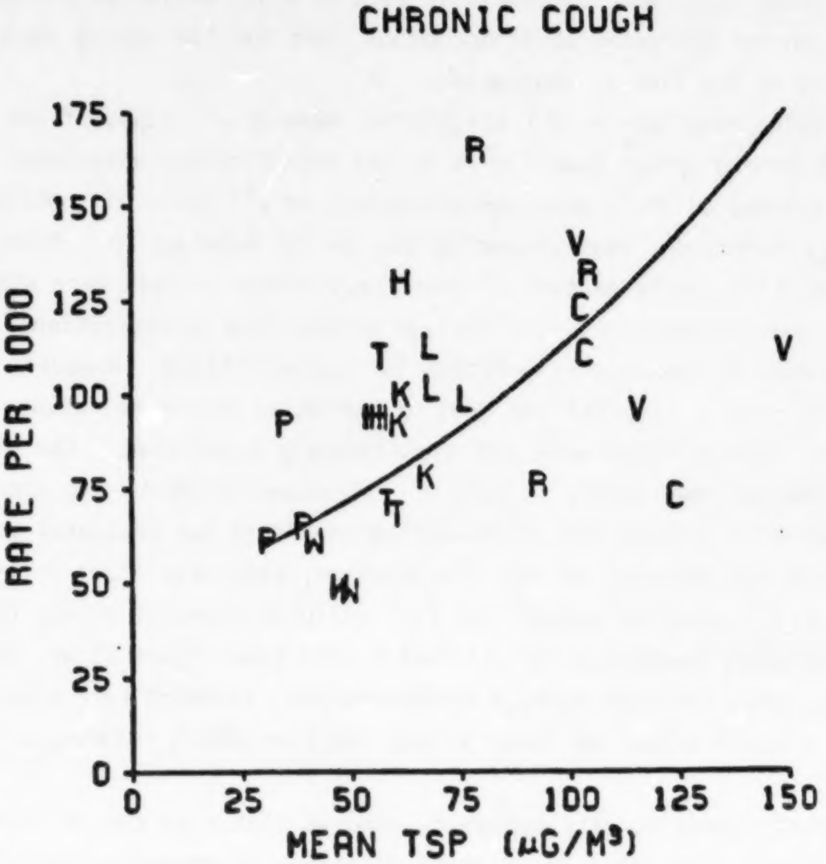

Figure 5 Adjusted frequency of cough for the 27 region-cohorts from the Six-Cities Study at the second examination plotted against mean TSP concentration during the previous year, with between-cities regression equation. LEGEND: P=Portage, T=Topeka, W=Watertown, C=Carondolet, L=Other St. Louis, R=Steubenville Ridge, V=Steubenville Valley, K=Kinston, H=Harriman.

Source: Ware et al. (1985).

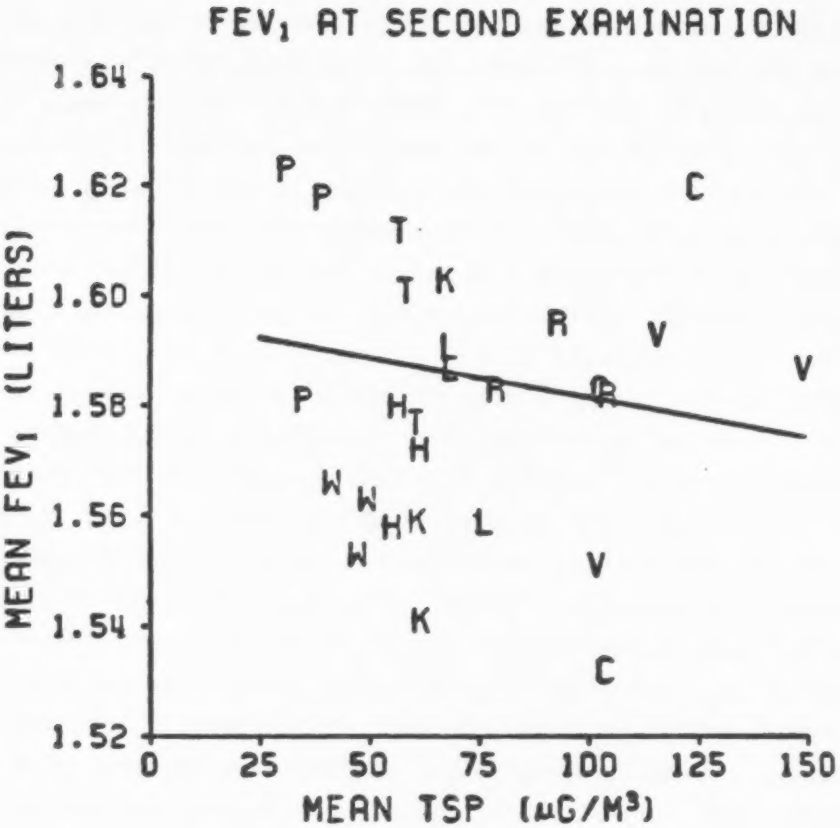

Figure 6 Adjusted mean percent of predicted FEV$_1$ at the first examination for the 27 region-cohorts from the Six-Cities Study plotted against mean TSP concentration during the previous year, with between-cities regression equation. The slope is not significantly different from 0. LEGEND: See Figure 4.

Source: Ware et al. (1985).

the analyses (e.g., TSP, etc.) may provide a "diluted" measure of exposure to the most highly toxic PM components (e.g., FP or small coarse-mode particles). In fact, the reported stronger associations between TSO_4 levels and other measures of ambient air FP concentrations are highly suggestive of possible associations between health effects observed in the Ware et al. (1985) study and exposure to small particles in contemporary U.S. atmospheres. Available data (Spengler and Thurston, 1983) from air monitors sampling inhalable particulates (IP; <15 μm) in the same cities included in the Harvard Six Cities Study analyses discussed here indicate IP mass annually averaged from approximately 20 to 60 $\mu g/m^3$. This suggests that the observed health effects noted above may be associated with annual average IP (<15 μm) concentrations below 60 $\mu g/m^3$. However, full interpretation of the strength and significance of these findings is difficult at this point, in light of further follow-up of these children still being in progress and the expectation that longitudinal analyses will later be carried out which will relate health data to more extensive aerometric data (including such data collected in later years).

In another new American study, by Schenker et al. (1983), respiratory symptom questionnaires were administered to 5557 adult women in a rural area of western Pennsylvania. Air pollution data (including SO_2 but not PM measurements) were derived from 17 air monitoring sites and stratified in an effort to define low, medium and high pollution areas. The means of 4-yr (1975-1978) annual average SO_2 levels in each stratum were 62, 66, and 99 $\mu g/m^3$, respectively. Risks for respiratory symptoms were assessed by a multiple logistic model that controlled for several potentially confounding factors (e.g., smoking) and used estimated air pollution concentrations at population-weighted centroids of 36 study districts (i.e., the concentrations were derived from another model which weighted observed monitoring data for distance from the district centroid and corrected for terrain effects). The risk of "wheeze most days or night" in nonsmokers residing in the high- and medium-pollution areas was 1.58 and 1.26 ($p = 0.02$), respectively, in relation to the low-pollution area. For residents living in the same location for ≥ 5 yr, these relative risks were 1.95 and 1.40 ($p < 0.01$), and increased risk of grade 3 dyspnea in nonsmokers was associated with SO_2 levels at $p \leq 0.11$. However, no significant association was observed between cough or phlegm and air pollution variables. The results of this study, while suggesting that wheezing may be qualitatively associated with ambient exposure to SO_2, are difficult to accept in light of:

(1) the very limited gradient of annual-average SO_2 levels across which health effects were reported to have been detected (associations with higher level exposures versus distinctly lower SO_2 concentrations would be more credible); (2) the very rough estimation of SO_2 exposure concentrations by means of model calculations; and (3) the lack of evaluation of possible PM or short-term SO_2 peak contributions to the evaluated health effects.

Several other recent studies have been reported that evaluated PM and/or SO_x effects in populations residing in the southwestern United States. In one, Chapman et al. (1983) conducted a survey in early 1976 regarding the prevalence of persistent cough and phlegm (PCP) among 5,623 young adults in four Utah communities stratified to represent a gradient of sulfur oxides exposures. Community-specific mean SO_2 levels had been 11, 18, 36 and 115 $\mu g/m^3$ during the 5 years prior to the survey and corresponding mean sulfate levels were 5, 7, 8, and 14 $\mu g/m^3$. No gradients of TSP or suspended nitrates were observed across the communities. Aerometric data were obtained from monitors sited at ground level. Differences along the sulfur oxides gradient were tested by chi-square statistics, and data were also analyzed by constructing categorical logistic regression models that treated PCP as the dependent variable and controlled for numerous potentially important factors (e.g. smoking, age, SES, etc.). For nonsmoking mothers, PCP prevalence was 4.2 percent in the high-exposure community and ~2.0 percent in all other communities. For non-smoking fathers, the PCP prevalence was 8.0 percent in the high pollution community and 3.0 percent elsewhere, while the PCP prevalence was less strongly associated with ambient sulfur oxides exposures for smoking fathers. Overall, intercommunity prevalence differences were significant at $p < 0.05$ for all the above groups except smoking fathers. The categorical logistic regression model yielded similar results, providing evidence suggestive of increased cough and phlegm being associated with annual average 115 $\mu g/m^3$ SO_2 levels and/or 14 $\mu g/m^3$ sulfate levels. There is much to argue for acceptance of the reported results from this study, including use of aerometric data from monitors situated in close proximity to study subjects' homes and nearly equivalent response rates on the health questionnaire across the communities sampled.

Dodge (1983) studied the respiratory health and lung function of Anglo-American children (grades 3 to 5) residing in an Arizona smelter community versus such children residing in another small Arizona community free of smelter air pollution. Cough prevalence was 25.6 percent in the smelter town children and 14.3 percent in the non-smelter groups ($p < 0.05$). Baseline pulmonary function at the outset of the study was equal in the two groups, and over the four years of the study, lung function growth (measured in terms of FEV_1 after 4 yr. of study minus predicted FEV_1) was also equal between the two groups. During the study, annual average SO_2 levels were 55 and 48 $\mu g/m^3$ at company and state monitoring sites, respectively (highest 24-hr SO_2 levels were 611 and 524 $\mu g/m^3$, respectively, at the company and state sites). Annual average TSP was 28 $\mu g/m^3$ in the smelter community. These results suggest that smelter community children had more cough than the control group children but no evident differences in lung function. However, it is difficult to ascribe the reported effects specifically to SO_2 or TSP (although the very low levels of the latter are unlikely to account for the effects).

Dodge et al. (1985) more recently reported on a longitudinal study of children exposed to markedly different concentrations of SO_2 and moderately different levels of particulate sulfate ($SO_4^=$) in Southwestern U.S. towns. Four groups of subjects lived in two areas of one smelter town and in two other towns, one of which was also a smelter town. In the highest pollution area, the children were exposed intermittently to high SO_2 levels (peak 3-hr $\bar{x}$ exceeded 2,500 $\mu g/m^3$ or ~1.0 ppm) and moderate particulate SO_4 levels ($\bar{x} = 10.1$ $\mu g/m^3$). When children were grouped by the four observed pollution gradients, the prevalence of cough (measured by questionnaire) correlated significantly with pollution levels (trend chi-square = 5.6; $p = 0.02$). No significant differences occurred among the groups of subjects over 3 years, and pulmonary function and lung growth over the study were roughly equal over all groups. The results tend to suggest that intermittent high level exposures to SO_2, in the presence of moderate particulate sulfate levels, produced evidence of bronchial irritation (increased cough) but no chronic effect on lung function or lung function growth. It is difficult to quantitate the SO_2 levels specifically associated with the observed effects, although the intermittent high level exposures to ~1.0 ppm (3 hr averages) mentioned earlier are likely implicated. Note that SO_2 levels for the higher polluted smelter town annually averaged 103 ± 282 (S.D.) $\mu g/m^3$ (indicating wide variability in the one hr mean levels) versus 14 $\mu g/m^3$ in the lesser polluted town. Other measured air pollutants, e.g. TSP, differed little between the high and low pollution areas (24-hr TSP $\bar{x} = 52$ and 58 $\mu g/m^3$, respectively). The observation of increased cough but lack of lung function changes in children comports well with the findings of Ware et al. (1986).

Lebowitz et al. (1982) studied 117 families in Tucson, Arizona, selected from a stratified sample of families in geographical clusters from a representative community population included in an ongoing epidemiologic study. Both asthmatic and non-asthmatic families were evaluated over a two year period, using daily diaries; and the health data obtained were related to various indices of environmental factors derived from simultaneous micro-indoor and outdoor monitoring in a representative sample of houses for air pollutants, pollen, fungi, algae and climate. Macromonitoring of air pollutants and pollen was carried out simultaneously. The data were mainly evaluated in terms of statistical techniques employing contingency tables and frequency distributions using SPSS programs. Two-month averages of indoor TSP ranged from 2.1 to 169.6 $\mu g/m^3$. Cyclone measurements of respirable particulate (RSP) ranged from below readable limits up to 28.8 $\mu g/m^3$. CO and NO_x measurements were also taken, but no SO_2 monitoring was reported. Suspended particulate matter and pollen were reported to be related to symptoms in both asthmatics and non-asthmatics, but the authors reported that the statistical analyses used were all qualitative (becase of low sample size) and statistical significance was not computed.

In a recently published Canadian study, Pengelly et al. (1986) reported results for an ongoing study of associations between particle size and respiratory health in children of Hamilton, Ontario. From 1979 to 1982, a cohort of approximately 3500 elementary school children was studied by determining each child's health history and respiratory symptoms by means of a questionnaire administered to their parents. Also, pulmonary function tests were conducted on the children at school. Particle size and concentrations were determined by using two networks distributed across the city, one consisting of 7 to 9 Anderson 2000 Cascade impactors and another of 27 hi-vol TSP samplers. Smoking, use of gas for cooking, SES and other potentially confounding factors were assessed by parental questionnaire and controlled for in statistical analyses, i.e., stepwise multiple regression techniques (linear for continuous dependent variables and logistic for binary dependent variables).

In the present report, Pengelly et al. (1986) focused on two indicators of respiratory health (cough and bronchitis episodes) and two indicators of pulmonary function (peak expiratory flow or PF and MEF_{75}), both adjusted for body size. Logistic regression analyses found no significant associations between cough or bronchitis episodes and air pollution indices, correcting for other factors. Both peak flow and MEF_{75} (adjusted for height) were reported to be significantly associated with the presence of fine particles. However, the fine fraction (FF) was estimated by adding results for samples collected by the lower stages of a cascade impactor (nominally reflecting sizes <3.3 µm). Based on particle bounce problems associated with this impactor (see discussion in Chapter 1) and comparison measurements made by the authors in Hamilton between dichotomous fine (<2.5 µm) and the cascade FF, additional coarse material >3.3 µm was probably also included in the FF measured by Pengelly et al. (1985). Overall the FF mass was more than double the dichotomous sampler fine mass.

Also since preparation of the earlier criteria review (EPA, 1982a), additional analyses of health effects relationships to PM and SO_x air pollution in European cities have emerged. Some of the new European work includes longitudinal analyses reported by van der Lende et al. (1986) as being conducted in regard to evaluating relationships between prevalence of respiratory symptoms and pulmonary function decline and variations in air pollution in two areas of The Netherlands. That is, health measurements were obtained from cohorts of approximately 2000 men and women (aged 15 to 64 years), residing in a highly polluted area (Vlaardingen) or a non-polluted rural area (Vlagtwedde), with subjects being followed and examined at intervals of three years. Over the course of the study, air pollution levels (PM measured as British smoke, SO_2, etc.) remained consistently very low in the latter area, whereas pollution levels declined over time in the former, highly polluted area. Van der Lende et al. (1986) noted that in a previous publication, they reported both a significantly higher prevalence of respiratory symptoms in the polluted area and also a greater decline there in pulmonary function (based on four consecutive studies over a 9-year period). In the present update paper (van der Lende et al., 1986), further findings are provided regarding associations between respiratory symptoms and pulmonary function decline and air pollution after six consecutive studies covering a 15-year period. The results, termed "preliminary" by the authors, provide some indications of more respiratory symptoms and greater pulmonary function declines in the polluted area than the control, non-polluted area. However, as currently available, the reported results do not allow for any quantitative conclusions to be clearly drawn regarding PM levels associated with observed health effects.

In another study (PAARC, 1982a,b), relationships between atmospheric pollution and chronic or recurrent respiratory diseases were evaluated from 1974 to 1976 as part of a French national survey in 28 areas of 7 cities and a newly industrialized region. The following pollutants were measured: SO_2 (specific-SP and acidimetric-AF methods); suspended particles (smoke and modified OECD gravimetric methods); nitrogen oxides (NO and NO_2 measured by modified Griess-Saltzmann method); and sulfates (measured by colorimetry after reduction). Samples were obtained over 24 hr. periods, but for the gravimetric measures (48 to 96 h), from 1974-76 except for one summer month each year and except for the sulfates which were determined only during the last half of the study and only in one part of the study zones. Twenty-eight study zones were defined to include 2-4 groups of ~1000 people in different cities exposed to pollution that differed as much as possible in quality and quantity (estimated from earlier aerometric data from 1971-72). Zones included populations situated within 0.5 to 2.3 km ($\bar{x}$ = 1.3 km) of air monitoring stations located 2-4 m above ground level in the center of each zone. National meteorological services supplied climatic data (e.g., temperature and humidity) taken at a station best characterizing each city (usually an airport, sometimes far from the zones investigated), and laboratory analyses for the air pollutants measured were carried out by laboratories in each city studied but for sulfates done at a single laboratory. Means for daily data for the pollutants studied were calculated for 1974-76 (where values came from data accumulated over several days, it was assumed the pollution was the same on each day). The extreme mean daily concentrations from various zones were: 13 and 127 $\mu g/m^3$ for SO_2 (AF), 22 and 85 $\mu g/m^3$ SO_2 (Sp); 18 and 152 $\mu g/m^3$ (smoke); 45 and 243 $\mu g/m^3$ (gravimetric), 7 and 145 $\mu g/m^3$ (NO); and 12 to 61 $\mu g/m^3$ (NO_2).

As for health evaluations, ventilatory function was measured in both men and women aged 25 to 59 and children aged 6 to 10 and respiratory symptoms were ascertained by standardized questionnaire. The results presented by PAARC (1982a,b) were for ~20,300 subjects from 20 zones (response rates varied from 70 to >90 percent in the included zones). Analyses of covariance were used for FEV results and logistical regression for the analysis of symptoms scores, taking into account control factors such as smoking and socioeconomic status. It should be noted that efforts were made to standardize the health endpoint measurements by common training of personnel carrying out testing in various zones and use of standard protocols.

The results of the study were reported by PAARC (1982b) as follows: (1) among both male and female adults, SO_2 concentrations are significantly associated with the prevalence of lower respiratory disease (LRD) symptoms; (2) among children, SO_2 is associated with the prevalence of upper respiratory disease (URD) symptoms; (3) for both adults and children, $FEV_{1.0}$ varied negatively in relation to elevations in SO_2 levels; and (4) no other pollutants were associated with ventilatory function or the prevalence of respiratory symptoms. More specifically, SO_2 concentrations were significantly correlated ($r > 0.44$) with incidence of cough, expectoration, and LRD symptoms in men and with LRD incidence in women ($r = 0.49$); and SO_2 correlated ($r = 0.53$) significantly with URD in children. It was noted that, whereas the above results emerged from analyses including data drawn from across cities, the gradient of SO_2 effects on symptom rates was not always evident within the same city (an analogous situation to findings reported by Ware et al., 1985, from data from six American cities). Similarly, the gradients emerging from regressions across cities for relationships between SO_2 and $FEV_{1.0}$ measures for men ($r = -0.52$), women ($r = -0.67$) and children ($r = -0.70$) were not always evident from data within all individual cities. In contrast to the SO_2 results, very mixed correlations (some positive and some negative, but none significant) were found between symptoms and measures of PM (smoke or gravimetric) and nitrogen oxides (NO, NO_2). Also, oddly, the correlations between $FEV_{1.0}$ and PM or nitrogen oxides measures were positive (some significantly so for NO or NO_2); i.e., they implied improved lung function as airborne particle or nitrogen oxides levels increased.

The results from the PAARC (1982a,b) study are interesting but challenging in terms of interpretation. The study appears to have ensured that aerometric data from the sampling stations used would be reasonably well representative of the surrounding study populations in the various zones, a definite strong point of the study. Similarly, efforts to standardize measurements of health endpoints across the different cities is another strong point. Also, in the case of the SO_2 measurements, analytical techniques were used and periodic intercomparisons made between laboratories such that the aerometric data and resulting correlations with symptoms and FEV decrements are probably credible. Much less confidence can be placed in the data derived for particulate matter, however, in view of the use of smoke readings and/or gravimetric readings that varied for 48 to 96 h periods as the basis for generating estimated particle concentrations to compare across cities. It is very dubious that an adequate comparison could be made, then, across cities in terms of relationships between either symptoms or pulmonary function measures and PM estimates; analyses relating such health endpoints to PM measures within individual cities (not reported in PAARC, 1982a,b) might be more credible, but this remains to be evaluated. The very anomalous results obtained for nitrogen oxides are difficult to explain or understand without more in-depth evaluation of specific aspects of the NO_x aerometric measurement methods as they were applied in the present study. Clearly, the results obtained for the nitrogen oxides are not believable in light of other existing literature.

In another European study (CEC, 1983) reported since the 1982 EPA criteria document was prepared, various health endpoints in children (6-11 yrs old) were evaluated in relation to air pollution in 19 geographic areas located in several different European Community countries. Data were obtained on 22,337 children and included information on respiratory symptoms obtained by questionnaire and pulmonary function measurements (peak expiratory flow rate measured by Wright peak flow meters). Efforts were made to standardize health measurements and protocols across all study areas. SO_2 concentrations were determined (using six different analytical methods) and particulate pollution was measured by smoke methods in some countries and by unspecified gravimetric methods in a few other ones. Side by side monitors were set up at 20 sites to help provide a basis for calibration across sites; these 20 "comparison" monitoring stations standardly used the British smoke method for PM and acidimetric method for SO_2. Significant associations emerged from analyses within some individual countries, but differed greatly from one country to another. In three countries, a composition variable called chronic non-specific lung disease (CNSLD) was highly significantly correlated positively with smoke, but the magnitude of the effects differed by a factor of about seven. The range of annual smoke levels was about the same in all three countries, about 15-40 $\mu g/m^3$. In four countries, there were significant associations with SO_2, but two of these were negative. In those with positive correlations annual median SO_2 levels were 60-160 $\mu g/m^3$, and for those with negative associations they were 20-120 $\mu g/m^3$, making it likely that the SO_2 results reflected chance variations rather than actual pollution effects. However, no significant relationships between health effects and particulate pollution were found when data from across countries were pooled. The reported results are difficult to interpret. The CEC (1983) report noted that annual average levels of smoke greater than 140 μg/m^3 in the presence of SO_2 at $\geq$180 μg/m^3 have been found by other studies to be levels above which consistent positive associations between health effects and air pollution are detectable. These levels are higher than any measured in the present study, and this might explain the lack of consistent effects observed from city to city or when data were analyzed across all cities. The results of analyses for data within a given city may warrant further, more detailed evaluation and may yield useful information on quantitative exposure-effect relationships. However, given the great difficulty noted by the CEC (1983) report in deriving bases for comparing air quality measurements for PM and SO_2 across different cities it is dubious that useful quantitative conclusions can be drawn from analyses of data combined across cities. This is especially the case in view of only limited calibration of smoke readings against gravimetric measurements by collocated gravimetric devices in the various countries.

Mühling et al. (1985) also studied the relationship between croup and obstructive bronchitis of German children taken to clinic versus the level of air pollutants of their residential areas. They show in this retrospective study that the incidence of these two diseases was greater in the area with higher SO_2 and dustfall levels. Several important confounding factors were examined (i.e., infection incidence, meteorological parameters, social status, and distance from clinic). Quarterly average values of SO_2 and dustfall were provided by the county of Nord Rhein in Westphalia. The authors state that their results clearly show that the disease frequency depended on whether the children lived in an area of high or low SO_2 and dustfall levels, but noted that it cannot be clearly stated whether or not the measured emissions are the actual cause of any increased morbidity.

Wojtyniak et al. (1984) using a multivariate analysis method showed that among men reporting persistent cough or phlegm, the prevalence of exacerbation of these symptoms was much greater in residents of more highly polluted parts of Cracow, Poland. In women, the prevalence of exacerbation of symptoms was associated with indoor air pollution resulting from coal combustion from coal stoves. This extensive longitudinal survey used questions based on the MRC questionnaire. An extensive monitoring network of 20 sampling stations covered the entire area of the city. Most important confounding factors were examined.

In summary, of the numerous new studies published on morbidity effects associated with long-term exposures to PM or SO_x, only a few provide potentially useful results by which to derive quantitative conclusions concerning exposure-effect relationships for the subject pollutants. The Ware et al. (1985) study, for example, provides evidence of respiratory symptoms in children being associated with particulate matter exposures in contemporary U.S. cities without evident threshold across a range of TSP levels for ~25 to 150 µg/m^3. The increase in symptoms appear to occur without concomitant decrements in lung function among the same children. The medical significance the observed increased in symptoms unaccompanied by decrements in lung function remains to be fully evaluated but is of likely health concern. Caution is warranted, however, in using these findings for risk assessment purposes in view of the lack of significant associations for the same variables when assessed from data within individual cities included in the Ware et al. (1985) study.

Other new American studies provide evidence for: (1) increased respiratory symptoms among young adults in association with annual-average SO_2 levels of ~115 µg/m^3 (Chapman et al., 1983); and (2) increased prevalence of cough in children (but not lung function changes) being associated with intermittent exposures to mean peak 3-hr SO_2 levels of ~1.0 ppm or annual average levels of ~103 µg/m^3 (Dodge et al., 1985).

Results from one European study (PAARC, 1982a,b) also suggest the likelihood of lower respiratory disease symptoms and decrements in lung function in adults (both male and female) being associated with annual average SO_2 levels ranging without evident threshold from about 25 to 130 µg/m^3. In addition that study suggests that upper respiratory disease and lung function decrements in children may also be associated with annual-average SO_2 levels across the above range. Further analyses would probably be necessary to determine whether or not any thresholds for the health effects reported by PAARC (1982a,b) exist within the stated range of annual-average SO_2 values.

CHAPTER 4. CONTROLLED HUMAN EXPOSURE STUDIES OF SULFUR DIOXIDE HEALTH EFFECTS

Since the completion of the 1982 EPA criteria document (U.S. EPA, 1982a) and the first addendum to it (U.S. EPA, 1982c), numerous scientific articles have been published in the peer-reviewed literature or accepted for publication in regard to controlled human exposure studies providing important additional information pertinent to development of criteria for primary (health related) NAAQS for SO_2. This chapter of the present addendum summarizes and evaluates the newly available studies and discusses their relationship with certain other key studies and conclusions from Chapter 13 of the 1982 criteria document and the earlier addendum. Several of the key issues discussed in the previous addendum have been further investigated. Those discussed here are

(1) Differences in subject characteristics, medication, and restriction from medication which may have considerable impact upon the differences in results reported by different laboratories.
(2) Concentration (SO_2)-response relationships in sensitive individuals under various conditions of exercise activity level or other form of hyperpnea.
(3) Possible enhancement of SO_2-induced bronchoconstriction by cold and/or dry air and by mouthpiece breathing.
(4) Mechanisms of action of SO_2-induced bronchoconstriction in sensitive (asthmatic) individuals.

The majority of subjects used in the studies summarized in this addendum were asthmatic. Asthma is a heterogeneous disease classification which includes a broad range of subjects. The least severe asthmatic may have had asthma diagnosed by a physician during childhood (by an unknown set of criteria) and have been mainly symptom-free since childhood and rarely, if ever, requires medication. On the other end of the spectrum are individuals who may be on chronic bronchodilator therapy (theophylline), who may use chromolyn (disodium chromoglycate) prior to activity, and may also require steroids. Pulmonary function tests (spirometry and airway resistance) are used to define the clinical status of an asthmatic at the time the studies are performed. Since airway obstruction in asthma is variable and often intermittent, and given that the physiologic status is highly influenced by the quantity and type of medication being used, tests of lung function cannot be used alone to determine the severity of the disease at any one time.

In addition to the diversity of clinical status, there was a broad range of selection criteria used to define asthma in various laboratories and from study to study. In some of the early studies, a clinical definition of asthma (i.e., diagnosed by a physician) was the selection criterion. In an effort to provide more descriptive information about the subjects, other criteria such as a positive response (i.e, much more reactive than "normal" subjects) to a pharmacologic stimulus such as methacholine or histamine was used as a criterion for selection. A positive (bronchoconstriction) response to an exercise test (5 to 10 min at 85 percent of maximum) or to an SO_2 inhalation challenge was also used to select subjects. The use of these descriptive criteria is sometimes useful in comparing results between laboratories.

One further point which relates to severity of asthma is the ability of the subjects to safely withhold their medication for a particular period of time. There was considerable variation between laboratories in the duration of time for which certain types or general classes of medication were restricted.

A number of the characteristics of the subjects who participated in studies described in this addendum are summarized in Table 3 along with other information on aspects of protocols employed in the studies.

4.1. NORMAL SUBJECTS EXPOSED TO SULFUR DIOXIDE

The pulmonary function effects of SO_2 in normal healthy adult volunteers have usually been much less than those seen in SO_2-exposed subjects with clinically documented asthma. The newly available information supports this conclusion in general but also suggests that some mild effects which are of little if any acute health importance may be observed in normal subjects at concentrations below 5.0 ppm. The 1982 criteria document presented the conclusion that the probable lowest-observable-effects level in normal healthy

TABLE 3. SUMMARY OF ASTHMATIC SUBJECT CHARACTERISTICS FROM NEWLY AVAILABLE CONTROLLED HUMAN EXPOSURE STUDIES OF EFFECTS OF SULFUR DIOXIDE ON PULMONARY FUNCTION

									-------PRELIMINARY	CHALLENGES-------		
REFERENCE	AGE	NUMBER OF SUBJECTS M/F	BASELINE[5] SRaw $\bar{x}$ (RANGE)[1]	BASELINE[5] FEV1.0/FVC% $\bar{x}$ (RANGE)[1]	MAJOR MEDICATIONS	MEDICATION[2] EXCLUSIONS	MEDICATION[3] WITHHELD	ALLERGY HISTORY	REVERSIBILITY OF OBSTRUCTION	HISTAMINE METHACHOLINE	SO_2	EXERCISE INDUCED BRONCOCONSTRICTION
Bethel et al. 1983a	22-36	8/2	5.0 (3.4-7.2)	79(63-89)	---[4]		48 h	Y	Y	HIS	---	---
Bethel et al. 1983b	20-37	3/6	4.4 (1.7-7.2)	82(73-93)	---[4]		48 h	Y	Y	HIS	Y	---
Bethel et al. 1984	25-36	5/2	6.6 (3.4-13.8)	71(52-84)	---[4]		48 h	Y	Y	HIS	Y	---
Bethel et al. 1985	22-46	16/3	6.0 (3.1-10.6)	77(58-89)	---	---	12 h	MOST	Y	HIS	---	---
Hackney et al. 1984	$\bar{x}$=25±4	13/4	5.94 (±4.03 S.D.)	76(±13 S.D.)	Half on Broncho dilators	No Cromolyn No Steroids	study day 12 h	---	---	---	Y	---
Kehrl et al. 1986	20-30	10/0	4.8 (2.0-8.5)	76(61-87)	Broncho dilators	No Cromolyn No Steroids	48 h oral 12 h inhal.	TESTED[6]	---	MET	Y	---
Koenig et al. 1983b	12-16	6/3	---	---	Theophylline	---	4 h	Y	Y	---	---	Y
Koenig et al. 1985a	14-18	5/5	---	---	Theophyl. Albuterol	---	4 h	Y	Y	---	---	Y
Linn et al. 1982	18-30 x=23	13/11	4.3 (NA)	80(±10 S.D.) (lowest 59)	None	No Routine Medication	1 week	Y	---	MET	---	---
Linn et al. 1983a	18-30 x=23	15/8	4.9 (±2.0 S.D.)	78(±11 S.D.)	None	No Routine Medication	1 week	Y	---	---	Y	---
Linn et al. 1983b	19-31	14/10	5.2 (1.7-17.5)	76(58-100)	---	---	12 h	---	---	MET[7]	Y	Y

continued on following page

TABLE 3. SUMMARY OF ASTHMATIC SUBJECT CHARACTERISTICS FROM NEWLY AVAILABLE CONTROLLED HUMAN EXPOSURE STUDIES OF EFFECTS OF SULFUR DIOXIDE ON PULMONARY FUNCTION

									-------PRELIMINARY CHALLENGES-------			
REFERENCE	AGE	NUMBER OF SUBJECTS M/F	BASELINE[5] SRaw $\bar{x}$ (RANGE)[1]	BASELINE[5] FEV1.0/FVC% $\bar{x}$ (RANGE)[1]	MAJOR MEDICATIONS	MEDICATION[2] EXCLUSIONS	MEDICATION[3] WITHHELD	ALLERGY HISTORY	REVERSIBILITY OF OBSTRUCTION	HISTAMINE METHACHOLINE	SO_2	EXERCISE INDUCED BRONCOCONSTRICTION
Linn et al. 1984a	19-30	19/7	5.2 (1.5-17.5)	76(50-90)	---	---	12 h	---	---	MET[7]	Y	Y
Linn et al. 1984b	19-33	13/11	5.0 (2.9-8.3)	81(67-100)	5 Broncho Dilator	---	8 h inhaled 12 h oral 48 h antihist.	---	---	---	Y	Y
Linn et al. 1984c	18-33	12/2	5.2 (1.8-7.5)	75(51-87)	Occasional Bronchodil.	---	12 h	---	---	---	Y	Y
Linn et al. 1985a	19-33	13/9	5.0- (2.8-8.2)	80(67-100)	Occasional Bronchodil.	---	8 h inhaled 12 h oral 48 h antihist	---	---	---	Y	Y
Linn et al. 1985b (COPD)	49-68 $\bar{x}$=60	15/9	19.0 (NA)	47(27-70)	Regular Bronchodil.	---	4 h	---	---	---	---	---
Roger et al. 1985	19-34	28/0	6.7 (2.0-12.8)	73(56-89)	Broncho dilators	No Cromolyn No Steroid	12 h inhaled 48 h oral	Y[6]	---	MET	---	---
Schachter et al. 1984	$\bar{x}$=27±5	4/6	5.0 (±1.5)	NA	Broncho dilators	---	24 h	Y	---	MET[8]	---	---
Sheppard et al. 1983	22-36	4/4	7.6 (3.2-14.9)	75(51-91)		---	8 h inhaled 12 h oral 48 h antihist.	---	Y	HIST	Y	---
Sheppard et al. 1984	20-37	5/3	8.3 (4.0-18.5)	68(52-85)	Metaproterenol Albuterol Theophylline	---	48 h antihist. 24 h theophyl. 10 h sympath	---	Y	---	---	---
Snashall and Baldwin 1982	25-61	4	7.3	---	2 Cromolyn 1 Steroid	---	24 h var.	Y	---	---	---	---

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REFERENCE	AGE	NUMBER OF SUBJECTS M/F	BASELINE[5] SRaw $\bar{x}$ (RANGE)[1]	BASELINE[5] FEV1.0/ FVC% $\bar{x}$ (RANGE)[1]	MAJOR MEDICATIONS	MEDICATION[2] EXCLUSIONS	MEDICATION[3] WITHHELD	ALLERGY HISTORY	-------PRELIMINARY CHALLENGES------- REVERSIBILITY OF OBSTRUCTION	HISTAMINE METHACHOLINE	SO_2	EXERCISE INDUCED BRONCOCONSTRICTION
Tan et al. 1982	16-60	14/8	0.92 KPA/l/s	---	2 Cromolyn Symp-Bronch	---	12 h bronch 24 h chrom or steroid 72 h antihist.	Y	Y	---	---	---

[1] Range except ± SD where indicated.

[2] Subjects were excluded from the study if using this medication.

[3] Number of hours medication withheld before start of exposure.

[4] No chronic bronchodilator therapy (theophylline).

[5] Baseline SRaw and $FEV_{1.0}$/FVC ratio were taken from the subject characterization when available, otherwise from pre-exposure measurements.

[6] Subjects were given allergy skin tests.

[7] Most but not all subjects were tested - most of these were reactive.

[8] Methacholine reactivity determined afterward.

TABLE 3B. SUMMARY OF NORMAL SUBJECT CHARACTERISTICS FROM NEWLY AVAILABLE CONTROLLED HUMAN EXPOSURE STUDIES OF EFFECTS OF SULFUR DIOXIDE ON PULMONARY FUNCTION

Author	Age	N M/F	Baseline SR_{aw}	Baseline $FEV_{1.0}/FVC$	Allergy History	Challenges
Bedi et al., 1984	19-28	23/0	$\bar{x}$ = 7.41	0.70-0.96	---	---
Folinsbee et al., 1985	19-28	22/0	$\bar{x}$ = 7.63	$\bar{x}$ = .81	---	---
Kulle et al., 1984	21-34	10/10	$\bar{x}$ = 5.52	$\bar{x}$ = .83	N	MET
Stacy et al., 1983	(18-40)	231/0	4.77*	0.83*	N	---
Schachter et al., 1984	26.1	5/5	---	---	---	---

*Subset of the data.

subjects is 5.0 ppm SO_2 at rest. The first addendum to the criteria document further suggests that normal subjects are approximately one order of magnitude (i.e., tenfold) less sensitive to SO_2 exposure than asthmatics.

Bedi et al (1984) studied subjects exposed to 1.0 and 2.0 ppm SO_2 in an environmental chamber (22°C, 40 percent RH) for 2h ($\dot{V}_E$ = 40 L/min for 3 to 30 min exercise periods with intervening 10 min rest). In the initial 9 subjects tested at both 1.0 ppm and 2.0 ppm SO_2, these investigators reported a modest (10.3 percent) but significant increase in SRaw following both exposure concentrations. Further investigation with a total of 22 subjects at 1.0 ppm using the same protocol failed to substantiate this finding. Given the trivial increase in SRaw (well within daily variations), the finding in the initial group probably occurred by chance. Folinsbee et al. (1985) also reported exposure of normal subjects to 1.0 ppm SO_2 in a study in which the effects of combined exposure to ozone and SO_2 were examined. The exposure protocol for this study was the same as the Bedi et al. (1984) study and included many of the same subjects. There were no significant changes in forced expiratory spirometry or airway resistance as a result of 1.0 ppm SO_2 exposure reported for these subjects.

Stacy et al. (1983) exposed subjects to 0.75 ppm SO_2 alone and in combination with several particulate pollutants. During the 4-h exposures, subjects walked on a treadmill on two occasions ($\dot{V}_E$ approximately 55 L/min). There were no significant effects of this SO_2 (or SO_2 plus particulate) exposure on either forced expiratory spirometry or airway resistance.

Schachter et al. (1984) compared the responses of asthmatics and normals (4M, 6F) to SO_2. Three of the normals were reportedly atopic (i.e., they probably had some history of allergy). There were no significant effects in normal subjects at any of the concentrations tested (0.25, 0.50, 0.75, and 1.0 ppm SO_2). Measurements were made for 60 min following a 10-min bicycle exercise period ($\dot{V}_E$ estimated at 35 L/min by measurement at the same workload on another occasion) in SO_2; the SO_2 level was maintained for the first 30 min post-exercise. At the higher SO_2 concentrations (0.75 and 1.0 ppm) the subjects did experience upper respiratory symptoms (these included unpleasant taste and odor and sore throat, symptoms associated with extrathoracic airways).

Koenig and Pierson (1985) in a review of several studies from their laboratory reported a decline (6 percent) in $FEV_{1.0}$ following exposure to 1.0 ppm SO_2 in 8 healthy normal adolescents. These subjects were exposed via mouthpiece to either 1 ppm SO_2, 1 mg/m^3 NaCl aerosol, or their combination. Resting exposure of 30 min was followed by 10 min of exercise ($\dot{V}_E$ = 39.9 L/min). The apparent decrease in $FEV_{1.0}$ occurred 2 to 3 min following the exercise period in SO_2. However, the $FEV_{1.0}$ decrease following saline aerosol was 4 percent and the absolute post-exposure $FEV_{1.0}$ values were identical (i.e., 2.89 liters). Furthermore, the authors used repeated pair t-tests in their analysis without correction for multiple comparisons (e.g., Bonferroni). These data should be subjected to a more rigorous statistical analysis to ascertain their significance. Even if these $FEV_{1.0}$ data were statistically significant, the differences between the air exposure and SO_2 exposure are so small that they are of no clinical importance.

Exposure to a mixture of SO_2 (1 ppm) and ammonium sulfate (528 μg/m^3) was studied in 20 normal subjects by Kulle and associates (1984). The subjects were young adult nonsmokers (10M, 10F) with normal spirometry and no allergic or respiratory disease history. Four hour exposures occurred in an environmental chamber (22°C, 60 percent RH) and included two 15-min exercise periods (mild-100 watts, $\dot{V}_E$ estimated 40 L/min [4 to 5 times rest]). There were no significant effects on spirometry or airway resistance after exposure to either SO_2 alone, ammonium sulfate alone, or their combination. There was no change in the response to a methacholine inhalation challenge following any of the exposures. There were reports of upper respiratory symptoms which were most prevalent with the combination exposure. This study further supports the absence of pulmonary function effects of SO_2 at 1.0 ppm in normal subjects.

Wolff et al. (1984) exposed nine steel workers, two of whom were classified as asthmatic, to 5 ppm SO_2 or SO_2 plus carbon dust for 2.5 h in an environmental chamber (22°C, 50 percent RH). The exposure included five 4-min exercise periods ($\dot{V}_E$ not reported). Mucociliary clearance measurement exhibited no consistent pattern of change. Histamine reactivity (percent drop in $FEV_{1.0}$ at threshold dose) showed a tendency to increase slightly (37 percent; 28 percent excluding asthmatics). There were no notable changes in pulmonary function among the normal subjects. Symptomatically the subjects found the SO_2 plus carbon dust exposure more unpleasant than SO_2 alone.

In summary, these studies of SO_2 exposure in normal healthy adults and adolescents demonstrate minimal, if any, significant pulmonary function effects of SO_2 exposure at 0.25 to 2.0 ppm with exposure durations ranging from 10 minutes to four hours including exercise periods, with work outputs sufficient to increase ventilation to 35 to 55 L/min. The only effect of any consequence was the increase in upper respiratory symptoms, which was chiefly the result of the unpleasant taste/odor of sulfur dioxide.

4.2 CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS EXPOSED TO SO_2

In addition to studies of asthmatics, Linn et al. (1985b) have studied 15 patients (ages 49 to 68) with COPD (mild to severe -- airway reactivity and reversibility not characterized) exposed to SO_2 (0.4, 0.8 ppm). One-hour exposures in an environmental chamber (22.5°C, 86 percent RH) included two 15-min exercise periods ($\dot{V}_E = 18$ L/min). In contrast to many previous studies of mild asthmatics, most of these patients regularly used bronchodilators and were permitted their use up to 4 h prior to study. There were no effects of SO_2 exposure in this subject group and no trends indicative of change in any of the measured functions (including SRaw, spirometry, and arterial oxygen saturation). It should be noted that little if any effect would be anticipated in asthmatics under these exposure conditions. The authors suggested that these COPD patients may be less reactive to SO_2 than younger asthmatics, although, as the authors discuss, given the low dose rate of exposure and the marked differences in medication status, this conclusion may be premature. The ventilations achievable by COPD patients are limited by the severity of their disease. It is conceivable that patients with less severe COPD able to exercise at a higher intensity and able to withhold medication may demonstrate responses to SO_2 which are similar to or even greater than those of young asthmatics.

4.3 FACTORS AFFECTING THE PULMONARY RESPONSE TO SO_2 EXPOSURE IN ASTHMATICS

4.3.1 Dose-Response Relationships

Important considerations in assessing the response to any inhaled gas or aerosol include the concentration of the substance in the inspired air, the rate of exchange of ambient air with the lung (ventilation), and the duration of exposure. The concentrations to which asthmatics have been exposed in more recent studies (since 1981) range from 0.10 to 2.0 ppm SO_2 although interest has focused on the range from 0.2 to 1.0 ppm. A broad range of exposure durations has been utilized ranging from 3 min to 6 h, although the primary focus has been on 5 to 10-min exposures which incorporate hyperpnea. Ventilation rates have ranged from 8 to 10 L/min at rest to 60 to 70 L/min (exercise or voluntary eucapnic hyperpnea), although most interest has centered on moderate ($\dot{V}_E$ = 35 to 50 L/min) to heavy ($\dot{V}_E$ > 50 L/min) exercise levels which in warm humid environments provoke, at most, only mild to moderate exercise-induced bronchoconstriction. Results from the recently published studies are summarized in Table 4.

Schachter et al. (1984) performed a concentration-response study in a group of 10 normal subjects (see Section 4.1 above) and a group of 10 asthmatic subjects exposed in an environmental chamber (23°C, 70 percent RH) to 0, 0.25, 0.50, and 1.0 ppm SO_2. Subjects rested briefly and then exercised for 10 minutes at 450 kpm ($\dot{V}_E$ = 35 L/min). In addition, subjects were exposed to 1.0 ppm SO_2 at rest. A significant decline in $FEV_{1.0}$ followed both the 0.75 (-8.3 percent) and 1.0 (-13 percent) ppm exercise exposures in these asthmatics. This was accompanied by a significant increase (54 to 68 percent at 1.0 ppm) in airway resistance (interrupter method). There were also some changes (these did not occur consistently at all concentrations or time intervals after exposure) in maximum expiratory flow which mainly occurred at the two highest concentrations. The recovery was rapid and pulmonary function was within 5 percent of baseline (and no longer significantly different) by 10 min postexercise even though SO_2 exposure continued. As other investigators have reported, there was a considerable range of response among these subjects, with 3 or 4 subjects demonstrating no appreciable response to SO_2 at any concentration while some others showed trends indicative of a dose-response (SO_2-$FEV_{1.0}$) relationship beginning as early as 0.25 ppm. The responses of asthmatics seen in this study may appear less severe than those seen by other investigators at similar SO_2 concentrations, although comparisons are difficult because of the different measurements made; the relatively small changes in Raw may be partially due to the use of the interrupter method. However, a number of other factors could account for the discrepancies between this and other recent studies of asthmatics. First, the subjects were not pre-selected for the presence of airway hyperreactivity to SO_2, cold air, exercise, histamine or methacholine, an approach frequently used by others. Second, the moderate workload and unencumbered oronasal ventilation probably resulted in a lower SO_2 delivery to the reactive airways than would occur with mouth breathing.

TABLE 4. SUMMARY OF RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF PULMONARY FUNCTION EFFECTS ASSOCIATED WITH EXPOSURE OF ASTHMATICS TO SO_2

Conc.	Duration	Number of Subjects*	Exposure Mode	Exposure Status	Observations	Comments	References
0.1 ppm	3 min.	8	Oral-mouthpiece 22°C 0% RH AH < 1	Hyperventilation to V_E = 51 l/min	Ventilation rate needed to increase SR_{aw} by 80% over resting baseline shifted by 3.8 l/min (7%) less than that needed for comparable HIB in dry air.	Symptom data not reported. Suggests marginal decrease in hyperventilation needed to produce HIB in dry air. Health significance unclear.	Sheppard et al. (1984)
0.2 ppm	5 min.	23	Chamber- 23°C 85% RH AH = 17.5	Exercising V_E = 48 l/min	No significant change in SR_{aw}, FEV_1, FVC, PEFR, $V_{max25-75}$ over exercise control. Possibly statistically significant increase in overall symptom score but not for any one symptom.	No measureable physiologic changes with possible increase in symptom scores of uncertain significance.	Linn et al. (1983b)
0.2 ppm	5 min.	8	Chamber- 5°C 1) 50% RH AH = 3.4 2) 85% RH AH = 5.8	Exercising V_E = 50 l/min	No significant changes in SR_{aw}, FEV_1, FVC, SG_{aw} over exercise control for either RH level. Suggestion of small increase in symptoms but no statistics given.	No measureable enhancement of SO_2 response for 5°C, 50% RH. Symptom score results of uncertain significance.	Linn et al. (1984)a
0.25 ppm	10 to 40 min.	10	Chamber- 23°C 70% RH AH = 14.4	Exercising V_E = 35 l/min	No significant changes in R_{aw}, FEV_1, MEF_{40}, with small (4%) change in V_{max50}. No clear increase in symptoms, suggestion of increased response in 2 of 10 subjects.	Indicates no effect. Changes even in sensitive subjects of uncertain health significance.	Schachter et al. (1984)
0,25 ppm	5 min.	1) 19 2) 9	Chamber 23°C D.P. = 7.6°C (36% RH) AH = 7.4	Exercising 1) V_E = 60 l/min estimated (750 kpm-min) 2) V_E=80-90 l/min estimated (1000 kpm-min)	With 750 kpm/min exercise, increase in SRaw in SO_2 (mean = 134%) signif. greater than clean air (mean = 77%). At 1000 kpm/min, no sig. diff. between SO_2 and clean air.	Effects at this level small or non-existent in comparison to heavy exercise alone. No symptoms reported. Response highly variable. Suggests 0.25 close to threshold for bronchoconstriction.	Bethel et al. (1985)
0.25 ppm	10 min. to 75 min.	28	Chamber 26°C 70% RH AH = 17.1	Intermittent exercise (3 10 minute periods) V_E = 42 l/min	No significant changes in SR_{aw}, TGV, resistance impedence for any of measurement periods. No significant changes in symptoms.	No measurable physiological or symptoms changes seen with .25 ppm SO_2 at this exercise level.	Roger et al. (1985)

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TABLE 4. SUMMARY OF RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF PULMONARY FUNCTION EFFECTS ASSOCIATED WITH EXPOSURE OF ASTHMATICS TO SO_2 (CONTINUED)

Conc.	Duration	Number of Subjects	Exposure Mode	Exposure Status	Observations	Comments	References
0.25 ppm	3 min.	8	Oral-mouthpiece 22°C 0% RH AH = <1	Hyperventilation to V_E = 51 l/min	Ventilation needed to increase SR_{aw} by 80% over resting baseline shifted to 5.6 l/min (10%) less than that needed for comparable HIB in dry air.	Symptom data not reported. Suggests small decrease in exercise needed to produce HIB in dry air. Health significance unclear.	Sheppard et al. (1984)
0.3 ppm	5 min.	24	Chamber 80% RH 1)-6°C 2) 7°C 3) 21°C 1) AH = 2.5 2) AH = 6.2 3) AH = 14.7	Exercising V_E = 50 l/min	At-6°C, SR_{aw} increased 94% in air and 105% in SO_2. At 7°C SR_{aw} increased 59% in air and 87% in SO_2. At 21°C SR_{aw} increased 28% in air and 59% in SO_2. Increase in symptom scores at all temperatures slightly greater in SO_2 than in air.	Significant main effects at 0.3 ppm not reported. Symptom score changes generally mild and of uncertain significance to health. Under test conditions, results indicate SO_2 and moist cold air effects are additive or less than additive.	Linn et al. (1984)b
0.4 ppm	5 min.	23	Chamber 23°C 85% RH AH = 17.5	Exercising V_E = 48 l/min	Increased SRaw in SO_2 (69%) sig. diff. than increase in clean air (35%). Significant decrements in V_{max} (25-75) (mean=10%), but no significant changes in FEV_1. Significant increase in overall symptom score, but only one of 12 symptom categories increased significantly. One subject required medication to relieve distress.	Indicates moderate broncocontriction. Overall symptom changes mild, but in at least one subject responses suggestive of clinical significance.	Linn et al. (1983)b
			5°C 1) 50% RH 2) 81% RH 1) AH = 3.4 2) AH = 5.8	V_E = 50 l/min	graphical depiction) and symptom score over exercise alone. Symptom score increase clearly larger for 50% RH than for 81% RH.	Significance of SG_{aw} and FEV_1 at 0.4 ppm not reported; indicates subjective response enhanced for dryer cool air even when measure of functional changes comparable to moist air.	

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TABLE 4. SUMMARY OF RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF PULMONARY FUNCTION EFFECTS ASSOCIATED WITH EXPOSURE OF ASTHMATICS TO SO_2 (CONTINUED)

Conc.	Duration	Number of Subjects	Exposure Mode	Exposure Status	Observations	Comments	References
0.4 ppm	5 min.	8	Chamber	Exercising	Apparent increase in SR_{aw} (from	No stat. for SR_{aw} changes.	Linn et al. (1984)a
0.5 ppm	10 to 40 min.	10	Chamber 23°C 70% RH AH = 14.4	Exercising V_E = 35 l/min	No significant changes in R_{aw}, FEV_1, MEF 40 with small (mean = 6%) decrement in V_{max50}. No clear increase in symptoms. Suggestions of increased FEV_1 response in 2 or 3 subjects.	Indicates minimal constriction for group at this exercise rate.	Schachter et al. (1984)
0.5 ppm	5 min.	10	Chamber 23°C 41% RH AH 8.4	Exercising V_E = 60 l/min estimated (750 kpm-min)	Increase in SRaw in SO_2 (mean = 238%) sig. diff. than increase in clean air (mean = 39%). Substantial variability in subjects; one showed eight-fold increase	Indicates substantial SO_2 induced bronchoconstriction at high exercise rate and mod. RH. No symptom data reported but extent of SR_{aw} changes suggestive of clinical significance.	Bethel et al. (1983)a
0.5 ppm	5 min.	9	80% RH, 23°C 1) Face mask 2) Mouthpiece AH = 16.5	Exercising 1) V_E = 27 l/min 2) V_E = 41 l/min 3) V_E = 61 l/min	Facemask exposure: No stat. sig. mean change in SR_{aw} with air or SO_2 at low or mod. exercise rate. For high exercise increase in SR_{aw} in SO_2 (219%) sig. larger than increase in clean air (25%) compared to mean baseline SR_{aw}. Percent ventilation breathed orally for the three exercise rates were: 1) 50%, 2) 52%, 3) 61%. Mouthpiece exposure: No sig. mean change in SR_{aw} for low exercise rate With moderate exercise, increased SR_{aw} in SO_2 (231%) sig. larger than clean air (5%). With high exercise, increased SR_{aw} in SO_2 (306%) sig. larger than clean air (25%).	Indicates SO_2 induced constriction enhanced by increased work rate, with protection afforded by oronasal (vs. oral) breathing greater at mod. than at high exercise rates. Asthmatics with rhinitis or other nasal blockage breathe more through mouth and appear at greater risk to SO_2 effects.	Bethel et al. (1983)b

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TABLE 4. SUMMARY OF RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF PULMONARY FUNCTION EFFECTS ASSOCIATED WITH EXPOSURE OF ASTHMATICS TO SO_2 (CONTINUED)

Conc.	Duration	Number of Subjects	Exposure Mode	Exposure Status	Observations	Comments	References
0.5 ppm	30 min. rest 10 min. exercise	9	22°C 75+% RH AH = 14.6+	Mouthpiece 5-6 x rest V_E	Mouthpiece exposure: $FEV_{1.0}$ decreased, -15% (-4% in air); R_T increased 47%; V_{max50}, V_{max75} decreased -30, -35%.	Indicates that mouthpiece breathing exacerbates the effect of SO_2 in asthmatics.	Koenig et al. (1983)b
		7		Facemask 5-6 x rest V_E	Facemask: No significant changes.		
0.5 ppm	30 min. rest 20 min. exercise	10 (14-18 yr)	22°C 75% RH AH = 14.6	Mouthpiece 43 l/min exercise	Increase in nasal resistance of 32%, but not significant. FEV_1 decrease -24%, V_{max50} -46%; V_{max75} -56%. R_T increased 60%.	Indicates SO_2 may cause increased nasal resistance in asthmatics, which may result in more oral breathing and consequently more bronchoconstriction.	Koenig et al. (1985)a
				Facemask	Significant increase in nasal resistance of 30%. FEV_1 decreased -16% V_{max50}, V_{max75} -26%		
0.5 ppm	10 min. to 75 min.	28	Chamber 26°C 70% RH AH = 17.1	Intermittent exercise (3 10 min. periods) V_E = 42 l/min	Increased SR_{aw} in SO_2 (93%) sig. larger than clean air (47%). SR_{aw} increase after second and third exercise periods sig. less than after first ex. period. No significant changes in FVC, FEV_1, FEF Group mean symptoms for 20 subjects not sig. increased. Substantial variability in subjects, with one showing 11-fold increase in SR_{aw} and requiring medication to relieve pronounced symptoms.	Extent of effects are decreased after short-term repeated exercise. Broad degree of sensitivity to SO_2 with about 25% of subjects showing a 100% increase in SR_{aw}. Symptoms in at least one subject of clear clinical significance.	Roger et al. (1985)

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TABLE 4. SUMMARY OF RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF PULMONARY FUNCTION EFFECTS ASSOCIATED WITH EXPOSURE OF ASTHMATICS TO SO_2 (CONTINUED)

Conc.	Duration	Number of Subjects	Exposure Mode	Exposure Status	Observations	Comments	References
0.5 ppm	3 min., repeated 3 times in succession at 30 min. intervals, again after 24 hrs and 1 week later	8	Oral-mouthpiece 23°C 82% RH AH = 16.9	Hyperventilation (varied for each subject)	Sig. increase in SR_{aw} ($\bar{x}$ = 104%) after first 3 min. exposure. After 30 min. rest, second response sig. but smaller (x = 35%); response after third exposure still smaller ($\bar{x}$ = 30%). SR_{aw} increase at 24 h. (x = 83%) and 1 week (x = 129%) not sig. diff. from increase after first 3 min. exposure.	Indicates repeated esposures to SO_2 can induce tolerance to bronchoconstrictive effects of SO_2 over a short period (>30 min) but not for longer periods.	Sheppard et al. (1983)
0.5 ppm	3 min.	7	Oral-mouthpiece 1) 23°C 77% RH 2) -11°C, "Dry" 1) AH = 15.8 2) AH < 1	Hyperventilation to "Threshold" V_E for each subject (30-50 l/min)	By design, increases in SR_{aw} or symptoms not sig. for SO_2 in warm, humidified air or cold dry air alone. Sig. increase in SR_{aw} ($\bar{x}$ = 222%) for combination of SO_2 and cold dry air. Six of seven subjects report wheezing and/or shortness of breath; two asked for medication. Symptoms not good indicator of of measured SR_{aw}.	Indicates that airway cooling, drying can increase SO_2 associated bronchoconstriction in hyperventilating asthmatics. Suggests synergism for these combinations.	Bethel et al. (1984)
0.6 ppm	5 min.	24	Chamber 80% RH 1) -6°C 2) 7°C 3) 21°C (1) AH = 2.5 (2) AH = 6.2 (3) AH = 14.7	Exercising V_E = 50 l/min	Increased SR_{aw} in SO_2 sig. greater than in clean air for all three temps. At -6°C, SR_{aw} increased 94% in air and 187% in SO_2. At 7°C, SR_{aw} increased 58% in air and 207% in SO_2. At 21°C, SR_{aw} increased 28% in air and 150% in SO_2. Symptom scores sig. greater in SO_2 than in air at all three temperatures.	Suggests that the bronchoconstrictive effects of cold air and SO_2 combine in an additive or less-than-additive fashion. Some suggestion of cold air-SO_2 interaction in total asthma score. SR_{aw} changes suggestive of clinical significance at all temperatures.	Linn et al. (1984b)

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TABLE 4. SUMMARY OF RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF PULMONARY FUNCTION EFFECTS ASSOCIATED WITH EXPOSURE OF ASTHMATICS TO SO_2 (CONTINUED)

Conc.	Duration	Number of Subjects	Exposure Mode	Exposure Status	Observations	Comments	References
0.6 ppm	5 min.	23	Chamber- 23°C 85% RH AH = 17.5	Exercising V_E = 48 l/min	Increased SR_{aw} in SO_2 (120%) sig. greater than in air (36%). Significant decline in FVC (mean = 3%), FEV_1 (mean = -13%), PEFR (mean = -26%) $V_{max25-75}$ x = -26%). Sig. increase in total symptom score; number of subjects with increased symptom score (21 of 23), and positive reading on discomfor meter (12 of 23), and in 4 individual symptom categories (cough, substantial irritation, wheezing and chest tightness). Three subjects required medication to relieve symptoms. No apparent effects next day or week.	Indicates bronchoconstriction Functional changes, symptoms indicate clinical significance.	Linn et al. (1983b)
0.75 ppm	3h 10 min. exer. at beginning	17	Chamber 22°C, 85% AH = 16.5	Exercising 45 l/min	No clean air control. With SO_2. SR_{aw} increased 263%, FEV_1 decreased 20% after exercise (SR_{aw} increased 322% in second series with no spirometry). Symptom scores increased after exercise. SR_{aw} and symptom scores were not significantly elevated after 1h of recovery in SO_2.	Indicates that recovery is complete for most subjects within 1h of SO_2 + exercise-induced bronchoconstriction.	Hackney et al.(1984)
0.75 ppm	10 min.	23	Chamber 23°C, 90% RH 1) oralnasal 2) mouthpiece AH = 18.5	Exercising V_E = 40 l/min	In clean air, SR_{aw} increased 54% by either oronasal or mouthpiece breathing. In SO_2, SR_{aw} increased 186% oronasal breathing and 321% by mouthpiece. Decline in FVC, FEV_1, PEFR, and $V_{max\ 25-50}$ for both exposure routes. Sig. increase in symptom score, both routes. SR_{aw} increase sig. greater for oral exposures; symptoms and other functional measure changes greater for oral, but not sig. so.	Indicates oronasal breathing ameliorates bronchoconstrictive effects of SO_2, but less effective against symptoms. Functional changes and symptoms indicate clinical significance.	Linn (1983)a

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TABLE 4. SUMMARY OF RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF PULMONARY FUNCTION EFFECTS ASSOCIATED WITH EXPOSURE OF ASTHMATICS TO SO_2 (CONTINUED)

Conc.	Duration	Number of Subjects	Exposure Mode	Exposure Status	Observations	Comments	References
0.6 ppm	5 min.	22	Chamber 21°C, 38°C 20% RH, 80%RH AH = 3.7, 14.7 @ 21°C AH = 9.3, 37.0 @ 38°C	Exercise V_E = 50 l/min	SR_{aw} changes in clean air ranged from -4% to +12%. With SO_2, at 21°C SR_{aw} increased 206% with dry and 157% with humid air, while at 38°C SR_{aw} increased 89% in dry air and 39% in humid air.	Indicates the importance of airway drying as an exacerbating factor in the induction of SO_2-bronchoconstriction.	Linn et al. (1985a)
0.6 ppm	Total 6 hr 2 successive days 2x5 min exer. each day, separated by 5h	14 (18-33)	Chamber 22°C 85% RH AH = 16.5	Exercise 50 l/min	After correction for clean air EIB, SR_{aw} increased 136, 120, 147, 100% on the early-day 1, late-day 1, early-day 2, late-day 2. No difference between times or days.	Indicates that refractory period for SO_2-induced bronchoconstriction is less than 5h.	Linn et al. (1984c)
0.6 ppm	5 min.	24	Chamber- 85% RH 1) 5°C 2) 22°C 1) AH = 3.4 2) AH = 16.5	Exercising V_E = 50 l/min	At 5°C, increased SR_{aw} with SO_2 (182%) sig. greater than clean air (38%). At 22°C, increased SR_{aw} with SO_2 (132%) sig. greater than clean air (27%). Lower respiratory and total symptom scores much greater in SO_2 than in clean air.	Suggests bronchoconstrictive effects of cold, moist air may increase SO_2 effects, but under these conditions, enhancement is inconsistent and not significant). Symptoms, SR_{aw} changes suggestive of clinical significance at both temperatures.	Linn et al. (1984a)
0.6 ppm	5 min.	8	Chamber- 5°C 1) 50% RH 2) 81% RH 1) AH = 3.4 2) AH = 5.8	Exercising V_E = 50 l/min Pilot study	Significant increase in SR_{aw} and symptom scores over exercise alone for both humidities (graphical depiction). No sig. diff. between humidities at this temperature.	Suggests that under these conditions, SO_2 response apparently not enhanced by lower humidity of cool air which has a low water content already.	Linn et al. (1984a)

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TABLE 4. SUMMARY OF RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF PULMONARY FUNCTION EFFECTS ASSOCIATED WITH EXPOSURE OF ASTHMATICS TO SO_2 (CONTINUED)

Conc.	Duration	Number of Subjects	Exposure Mode	Exposure Status	Observations	Comments	References
0.75 ppm	10 to 40 min.	10	Chamber- 23°C 70% RH AH = 14.4	Exercising V_E = 35 l/min	Significant changes in FEV_1, (mean = -8% MEF_{40} (mean = -22%), V_{max50} ($\bar{x}$ = -11%), and RAW (x = 40%). No sig. discomfort persisted 10 min. after exposure. Apparent large increase in lower airway symptom complaints. Wide variable responses among subjects.	Indicates bronchoconstriction Symptoms, functional changes and additive effects of clinical significance began between 0.5 and 0.75 ppm for this study group & conditions on average.	Schacter et al. (1984)
1.0 ppm	30 min. rest 10 min. exercise	9	22°C 75% RH AH = 14.6	Mouthpiece 5-6 x rest V_E (30-50 l/min)	FEV_{10} (-23%), V_{max50} (-51%), V_{max75} (-61%), R_T (+71%). Recovery was slower than after 0.5 ppm exposures.	Suggests that more severe SO_2-induced bronchoconstriction requires longer recovery than less pronounced changes at lower conc.	Koenig et al (1983)b
1.0 ppm	10 to 40 min.	10	Chamber- 23°C 70% RH AH = 14.4	Exercising V_E = 35 l/min	Significant changes in FEV_1 (mean = -14%), MEF_{40} (mean = 27%), V_{max50} ($\bar{x}$ = -22%), and RAW ($\bar{x}$ = -54%). No sig. decrements persist 10 min. after exposure. Apparent large concentration-related increase in lower airway symptom complaints. Three subjects apparently non-responsive (based on FEV_1) even at this conc., with at least one very sensitive subject showing > 50% FEV_1 decline.	Indicates bronchoconstriction. Symptoms and functional changes suggestive of clinical significance.	Schacter et al. (1984)
1.0 ppm	10 to 75 min.	27	Chamber- 26°C 70% RH AH = 17.1		Sig. decrease in SR_{aw} after all 3 exercise periods but response decreases with time. First Exercise: Increased SR_{aw} in SO_2 (190%) sig. greater than air (47%) Second Exercise: Increased SR_{aw} in SO_2 (147%) sig. greater than air (34%) Third Exercise: Increased SR_{aw} in SO_2 (116%) sig. greater than in air (30%). Group mean symptom analysis for 20 subjects showed sig. increase in shortness of breath and chest discomfort. Substant. variability in subject response; one unable to go beyond 35 min. point.	Respiratory impedence suggests SO_2 induced bronchoconstriction mostly in peripheral airways. Decreased response with time suggest short-term tolerance, but effects of clinical signicance occur even after third exercise period.	Roger et al. (1985)

continued on following page

TABLE 4. SUMMARY OF RESULTS FROM CONTROLLED HUMAN EXPOSURE STUDIES OF PULMONARY FUNCTION EFFECTS ASSOCIATED WITH EXPOSURE OF ASTHMATICS TO SO_2 (CONTINUED)

Conc.	Duration	Number of Subjects	Exposure Mode	Exposure Status	Observations	Comments	References
1.0 ppm	1) 10 mins., reported 3 times in succession with 15 minute intervals 2) 30 min. continuous exercise	10	Chamber 26°C 70% RH AH = 17.1	Intermittent Exercise V_E = 41 l/min	First Exercise: Significant increase in total SR_{aw} (x = 172%). Second Exercise: Sig. increase in total SR_{aw} (x = 137%. Third Exercise: Sig. increase in total SR_{aw} (x = 106%). Attenuation with time occurred in 4 of 10 subjects. Continuous Exercise: Sig. increase in total SR_{aw} (x = 233%) after 30 minutes	Indicates mechanism responsible for apparent tolerance to repeated short-term exposures to SO_2 does not reduce responses to continuous exercise for comparable time periods.	Kehrl et al. (1986)
.25 to 2 ppm	10 minutes, different days	27	Chamber 26°C 70% RH AH = 17.1	Exercise V_E = 42 l/min	Concentration response relationships for four exposures interpolated for each subject to determine $PC(SO_2)$, the SO_2 concentration producing a 100% increase in SR_{aw} over exercise in clean air. Cumulative plot shows 25% of subjects with $PC(SO_2) < 0.5$ ppm, median $PC(SO_2)$ was 0.75 ppm, and about 20% of subjects have a $PC(SO_2)$ of > 1.95 ppm.	Reflects additional analyses of data from first exposure period in experiment reported in Roger et al. (1985). Quantifies variability in response among asthmatics for functional changes of potential clinical significance. Suggests effects of concern in some subjects may extend to near 0.25 ppm.	Hortsman et al. (1986)
.125 to 2 ppm	3 minutes doubling exposures in succession with no breaks	8	Oral-mouthpiece 1) -20°C 0% RH 2) 22°C 0% RH 3) 22°C 70% RH 1) AH <1 2) AH <1 3) AH = 13.6	Hyperventilation to V_E = 30 to 40 l/min	By design, SR_{aw} increase for clean air alone not sig. Concentration response relationships for 4 to 5 exposures interpolated for each subject to determine PC_{100}, the SO_2 concentration producing a 100% increase over resting baseline. Mean PC_{100} for differing conditions were: Dry Cold Air - 0.51 ppm; Dry Warm, Air - 0.60 ppm; Humid Warm Air = 0.87 ppm; PC_{100} for humid warm air sig. greater than for dry cold or dry warm (which were not sig. diff. from each other.	Nature of doubling concentrations may have affected PC_{100} estimates. Results quantify wide variability among subjects. Indicates very dry air potentiates SO_2 bronchoconstriction regardless of temperature.	Sheppard et al. (1984)

AH = absolute humidity = g H_2O vapour/m^3 of air.

$g/m^3 = mg/\ell$.

HIB = Hyperventilation Induced Bronchoconstriction

In a subsequent paper, Witek et al. (1985b) described the symptoms experienced by the subjects in the Schachter et al. (1984) study. Both asthmatics and normal subjects experienced increased respiratory symptoms following SO_2 exposure. Normal subjects complained chiefly of upper airway (nose and mouth) symptoms of odor or unpleasant taste; these symptoms were not increased by exercise. Normals experienced no significant lower respiratory symptoms. There was an increase in lower respiratory symptoms in asthmatics at 0.75 and 1.0 ppm SO_2, although the significance of this trend is not clear ($p = 0.09$). Upper airway symptoms tended to be elevated in both asthmatics and normals, but more consistently in normals. The lower respiratory symptoms increased with exercise in the asthmatics and were significantly correlated ($r = 0.67$, $p <.05$) with the decrease in $FEV_{1.0}$. In contrast, exercise did not affect symptoms in normals. The authors stated that even the asthmatics' symptoms were generally mild and required no therapy.

Linn and coworkers (1983b) also evaluated the responses of naturally breathing asthmatics exposed to SO_2 in an environmental chamber (23°C, 85 percent RH) while performing 5 min of moderately heavy exercise ($\dot{V}_E = 48$ L/min). Twenty-three mild asthmatics (some of whom were hyperreactive to methacholine and all of whom were reactive to 0.75 ppm SO_2) were exposed four times, once each to 0, 0.20, 0.40, and 0.60 ppm. Significant increases in SRaw occurred after clean air exposure due to exercise-induced bronchoconstriction. The SRaw increase after 0.20 ppm was not significantly larger than after clean air, but the SRaw following exposure to the two higher concentrations was significantly elevated. SRaw demonstrated a significant trend to increase with increasing SO_2 concentration but this trend was not linear; the mean increases in SRaw after 0.2, 0.4 and 0.6 ppm SO_2, over those seen with clean air, were 0.54, 2.03, and 6.77 cm H_2O·sec. The response data are suggestive of a threshold concentration for response to SO_2. There is a strong possibility of a concentration threshold for SO_2 at low concentrations and ventilations since the scrubbing of SO_2 by the upper airway mucosal surfaces may be so efficient that only a relatively small quantity of SO_2 reaches the reactive portions of the airways.

Roger et al. (1985) studied 27 mild asthmatics (methacholine sensitive, not using cromolyn or steroid medication). Exposures were to 0.0, 0.25, 0.50, and 1.0 ppm SO_2 in an environmental chamber (26°C, 70 percent RH) utilizing natural breathing while performing treadmill exercise ($\dot{V}_E = 41$ L/min). The increases in SRaw post-exercise associated with these exposures were 48, 63, 93, and 191 percent respectively; the increases at the two highest concentrations were significantly greater than with air. The data reported by Roger et al. (1985) were further analyzed (Horstman et al., 1986) in order to determine individual SO_2-SRaw dose-response relationships. This analysis included previously unreported data on exposure to 2 ppm in subjects who were non-responsive to lower concentrations. From interpolation of the dose-response plots, the concentration of SO_2 which provoked a 100 percent increase in SRaw ($PCSO_2$) was determined for each subject. All SO_2 responses were corrected for the response observed with clean air, i.e., exercise-induced bronchoconstriction. For the most reactive 80 percent of the subjects the $PCSO_2$ ranged from 0.28 to 1.38 ppm; it was greater than 1.95 ppm (and therefore basically indeterminate) in the remaining 20 percent of subjects. (This percentage of SO_2-insensitive asthmatics is in general agreement with Linn et al., 1984b) The median $PCSO_2$ in all subjects and under these conditions was 0.75 ppm; 25 percent (i.e., 6) of the subjects had a $PCSO_2$ less than 0.50 ppm, the lowest being 0.28 ppm. The dose-response relationships relate only to the level of exercise used in this study. Different dose-response relationships would be expected for different exercise levels or different exposure durations.

4.3.2 SO_2-Induced Versus Non-Specific Airway Reactivity

It is well established that most asthmatics are highly reactive to bronchial inhalation challenge with histaminergic (histamine) and cholinergic (acetylcholine, carbachol, methacholine) agents. Clear evidence has also emerged that asthmatics are substantially more reactive to SO_2. The relationship between SO_2-induced bronchoconstriction and non-specific airway reactivity has been examined or alluded to in a number of studies (Horstman et al., 1986; Witek et al., 1985a; Sheppard et al., 1983). Airway reactivity to methacholine and to histamine are well correlated ($r = 0.70$) (Chatham et al., 1982). Methacholine reactivity was more highly correlated with exercise-induced bronchoconstriction and was better able to distinguish between normals and asthmatics (Chatham et al., 1982).

Witek et al. (1985a) reported that the methacholine reactivity of a group of 8 asthmatics was highly ($r = 0.86$, $p < 0.05$) correlated with their reactivity to SO_2. The subjects were a subgroup of 8 of the 10 subjects used in the Schachter et al. (1984) study (see Schachter et al., 1984, for protocol details). The dose of methacholine required to produce a 20 percent drop in the maximal expiratory flow at 40 percent VC above RV on a partial expiratory maneuver (MEF40 percent-P) was determined. From the MEF40 percnet-P vs. SO_2 response relationship, the SO_2 concentration required to produce a 20 percent drop was determined. The relationship between the methacholine provocative dose and the SO_2 provocative concentration was determined by rank correlation. This study suggests that there is a relationship between methacholine reactivity and severity of SO_2-induced bronchospasm.

On the other hand, Koenig and Pierson (1985) concluded in their recent review article that the response to a methacholine challenge was not a good predictor of the degree of SO_2-induced bronchoconstriction in asthmatics. They suggested that a positive response to an exercise challenge was more likely to predict a positive response to SO_2. Linn et al. (1983b) present subject data (their Table 1) for methacholine reactivity, exercise response (SRaw change), and SO_2 response (SRaw change), which are sufficient to allow calculation of correlation coefficients between these three variables. The rank-order correlation coefficient between methacholine reactivity and SO_2 response was 0.38, between exercise response and SO_2 response was 0.46, and between exercise and methacholine response was 0.47 (these calculations by the authors of the addendum). The latter two correlation coefficients were significant ($p < 0.05$) and this observation supports the suggestion of Koenig and Pierson (1985). Horstman et al. (1986) have compared the methacholine reactivity (interpolated dose causing a doubling of SRaw) with the SO_2 response ($PCSO_2$; see previous section). The methacholine and SO_2 responses were significantly but weakly correlated ($r = 0.31$).

The relationship of histamine reactivity to SO_2-induced bronchoconstriction is less well described. "Tolerance" to SO_2 exposure reported by Sheppard et al. (1983) was not accompanied by any decrease in histamine reactivity. However, this does not necessarily indicate the absence of an overall relationship between histamine reactivity and SO_2 responsiveness.

One problem in establishing the strength of the relationship between non-specific airway reactivity and SO_2 response is the restricted range of the observations in these studies which deal only with the most reactive segment of the population, namely asthmatics. Inclusion of data from normal subjects would undoubtedly result in a higher correlation. Nevertheless it is apparent that increased SO_2 responsiveness in asthmatics cannot simply be ascribed to elevated non-specific airway reactivity.

4.3.3 Oral, Nasal, and Oronasal Ventilation

For SO_2 in particular, but also for many other gases and aerosols, the inhalation route is an important factor in delivery of the substance to the lung. Since 1982, a number of studies have been reported which specifically address this issue. There are important interactions between the inhalation route, which in many cases is simultaneous oral and nasal breathing (oronasal) (Proctor, 1981), and the ventilation rate is such that the efficiency of the oral or nasal mucosa in absorbing SO_2 declines as the air flow increases. As noted in the previous addendum (U.S. EPA, 1982c) the studies of Kirkpatrick et al. (1982) and Linn et al. (1982b in the earlier Addendum I; 1983b in the present reference list) indicated the importance of oronasal airway scrubbing of SO_2 in mitigating the effects of SO_2 during nasal or oronasal breathing.

In an effort to further resolve the interaction between exercise ventilation and route of inhalation in asthmatics, Bethel et al. (1983b) studied 9 mild asthmatics breathing humidified air (23°C, 80 percent RH) through either a mouthpiece or a divided facemask (ventilation could be measured separately in nasal and oral chambers). Subjects worked at 250 ($\dot{V}_E$ = 26 L/min), 500 ($\dot{V}_E$ = 53 L/min), or 750 kpm ($\dot{V}_E$, 62 L/min) and breathed either clean air or 0.50 ppm SO_2 for 5 min. Mouthpiece inhalation of SO_2 resulted in increased SRaw at moderate (231 percent) and heavy (306 percent) workloads, but with facemask breathing, the SRaw only increased at the heavy workload (219 workload). The oral component of ventilation during mask breathing was approximately 38 L/min at the heavy workload, similar to the oral ventilation of 41 L/min with mouthpiece breathing at the moderate workload; the similarity of SRaw responses in these two cases is noteworthy. From these studies it is apparent that oronasal breathing ameliorates some of the effect of SO_2 breathing in asthmatics, but this effect becomes less important as the exercise workload increases and both the overall ventilation rises and the relative contribution of oral ventilation to total ventilation increases.

Kleinman (1984) has modeled the bronchoconstriction response to SO_2 in relation to ventilation, oral/nasal partitioning of ventilation, and differences in SO_2 scrubbing capability of the two upper airways. This model suggests that differences in response to SO_2 can be quantitatively accounted for by differences in penetration of SO_2 to target sites within the lower or thoracic airways (defined as structures at or just below the laryngopharynx).

Because of the possible interference with oral breathing during the facemask exposures, Bethel et al. (1983a) studied 10 mild asthmatics exposed to 0.50 ppm SO_2 in an exposure chamber (23°C, 80 percent RH) to determine if freely breathing subjects would develop bronchoconstriction at this concentration. Following 5 min exercise at 750 kpm ($\dot{V}_E$ unreported, approximately 50 to 60 L/min), SRaw increased 39 percent in clean air but increased 238 percent in 0.50 ppm SO_2 similar to that previously observed with facemask breathing. Thus mild asthmatics performing moderate to heavy exercise exhibited clear evidence of bronchoconstriction after 5 min exposure to 0.50 ppm SO_2 while breathing unencumbered.

In a subsequent study (Bethel et al., 1985), the effects of 0.25 ppm SO_2 were studied in 19 mild to moderate asthmatics using a similar protocol (23°C, 36 percent RH with 5 min exercise at 750 kpm). SRaw increased from 6.38 to 11.32 post-exercise in clean air and from 5.70 to 13.33 post-exercise in 0.25 ppm SO_2. The slightly greater response following SO_2 exposure was apparently significant ($p < 0.05$, Wilcoxon one-tailed sign test). The application of a signed rank test, preferable in this case, would not confirm this significance. However, when the workload was increased to 1000 kpm in 9 of the 19 subjects, the increase in SRaw after clean air exercise was slightly, but not significantly, greater than that after exercise with 0.25 ppm SO_2. The authors suggested that the threshold concentration of SO_2 which may cause bronchoconstriction in mild asthmatics under conditions of moderate to heavy exercise appears close to 0.25 ppm. However, the very small rise in SRaw at only one work output indicates that the additional effect of 0.25 ppm SO_2 (over that produced by exercise) is of minor, if any, clinical significance. Nevertheless, it must be stressed that these asthmatics had relatively mild disease.

Koenig et al. (1983b) examined the effects of exposure to 0.5 and 1.0 ppm SO_2 combined with a sodium chloride droplet aerosol in nine extrinsic adolescent asthmatics. Judging from their medication requirements, this group of asthmatics would have to be considered more severe than the adult asthmatics studied by several other investigators. The exposures were delivered via mouthpiece (22°C, 75+ percent RH) for 10 min during moderate treadmill exercise (30 min rest exposures were followed by 10 min exercise). The responses ranged from a 15 percent decrease in $FEV_{1.0}$ at 0.5 ppm to a 61 percent decrease in V_{max75} at 1.0 ppm. The response to 1.0 ppm tended to be greater but this difference between SO_2 concentrations did not attain overall statistical significance. Nevertheless, the effects of SO_2 on lung function persisted longer after the higher concentration exposure. $FEV_{1.0}$, V_{max50} and V_{max75} (partial flow volume curves) were significantly reduced and total respiratory resistance (forced oscillation) was significantly increased following mouthpiece breathing of 0.5 or 1.0 ppm SO_2. Seven of nine subjects were also exposed to 0.5 ppm SO_2 plus aerosol delivered via a facemask (ventilation 5 to 6 times rest or 30 to 50 L/min). The pulmonary function changes after breathing 0.50 ppm SO_2 plus aerosol via facemask were not significantly different from baseline. However, some of the subjects intentionally breathed through their nose rather than oronasally therefore the comparison of the results of this study with those of Bethel et al. (1983a) would not be appropriate.

Previous studies (Andersen et al., 1974) cited in the criteria document have suggested that nasal resistance increases following SO_2 exposure. Because this could have an important impact on the route of inhalation and/or the oronasal ventilation switch point, Koenig and associates (1985) examined the effects of 0.50 ppm SO_2 on the work of nasal breathing in a group of moderate adolescent asthmatics (7/10 were theophylline users). Subjects were exposed to SO_2 (and H_2SO_4 aerosol -- 100 $\mu g/m^3$) either via mouthpiece or oronasal facemask (22°C, 75 percent RH). Thirty min resting exposure was followed by 20 min of moderate exercise on a treadmill ($\dot{V}_E = 43$ L/min). Exposure to SO_2 via mouthpiece or facemask resulted in an approximate 30 percent increase in nasal work of breathing (measured with a divided diving mask containing two pressure transducers which measured the pressure drop across the nasal passages). Due to marked inter- and intra-individual variability in these nasal measurements, only the increase in nasal work of breathing after facemask exposure was found to be statistically significant. No increase occurred with clean air or sulfuric acid aerosol exposure. The decreases in $FEV_{1.0}$ and V_{max50} were significantly greater with mouthpiece than with facemask exposure to 0.50 ppm SO_2. The implications of this finding may be of considerable importance. A rise in nasal work of breathing could provoke a switch to predominantly oral breathing during exercise at a lower ventilation, thus causing more inspired air to traverse the oropharynx rather than the nasopharynx. Since oral inhalation of SO_2 results in greater increases in airway resistance and larger declines in spirometric tests, an increase in the proportion of oral ventilation due to nasal congestion could result in SO_2-induced bronchoconstriction at lower concentrations in freely breathing exercising asthmatics.

4.3.4 Time Course of Response to SO_2 in Asthmatics

Early studies of SO_2 exposure in normal healthy subjects indicated that the peak response occurred early in exposure and was reduced with continued exposure. The effect of prolonged or repeated exposure has recently been addressed in asthmatics.

Sheppard and associates (1983) reported the responses of mild to moderate asthmatics (n = 8) exposed three consecutive times to 0.51 ppm SO_2. The subjects performed voluntary eucapnic hyperpnea with 0.5 ppm SO_2 for 3 min at a ventilation which had previously caused bronchoconstriction (air temperature = 22.6°C, RH = 82 percent). Three subjects failed to reach the target of a 60 percent increase in SRaw above baseline and consequently performed additional hyperpnea to produce increased SRaw. Twice more, at 30-min intervals, the SO_2 hyperpnea was repeated. SRaw was measured before and after each SO_2 exposure. A single bout of SO_2 hyperpnea was performed on the following day and again one week later. The first exposure to SO_2 caused a doubling of SRaw (104 percent increase). The second and third SO_2 exposures elicited only modest increases in SRaw (35 percent, 30 percent respectively). However, 1 day and 7 days later, the response to SO_2 was similar (+89, +129 percent) to that on the first exposure.

In this study, the relationship of SO_2 tolerance to histamine-induced bronchoconstriction was examined in a subgroup of four subjects. A baseline histamine challenge test was followed 30 min later by two 3-min periods of SO_2 breathing separated by 30 min (as in the initial part of the study). When the histamine challenge was repeated after a further 30 min, the histamine dose-response relationship was unchanged despite the blunted response to SO_2 inhalation. This study demonstrated that repeated exposure of asthmatics to 0.5 ppm SO_2 by mouthpiece at 30-min intervals resulted in a blunted SO_2 response (tolerance) which persisted for at least 30 min but was absent after 24 h and was not associated with any change in airway reactivity to histamine. The implications of this study for response mechanisms are discussed in Section 4.3.

Linn et al. (1984c) also studied the effect of repeated SO_2 inhalation in 14 mild to moderate asthmatics who were exposed to 0.6 ppm SO_2 for 6 h on each of two consecutive days. These were compared with similar clean air exposures. They performed two 5-min bouts of exercise ($\dot{V}_E$ = 50 L/min), one immediately upon entering the exposure chamber (22°C and 85 percent RH) and a second bout 5 h later. SRaw was measured immediately post-exercise and at hourly intervals between exercise periods. With SO_2 exposure, SRaw was approximately doubled following each exercise bout. Small increases in SRaw also occurred following exercise in clean air. There were no differences in response between early and late exercise challenges and no significant differences in SRaw response between exposure days. SGaw, but not SRaw, responses indicated smaller decreases on the second SO_2 exposure day (-0.091 sec·cm H_2O) than the first (-0.119 sec·cm H_2O). This difference was of only marginal statistical significance and not of any clinical importance. The results of this study indicate that SO_2-exercise challenges separated by 5 h (between exercise periods) produce essentially similar responses and that the responses are not appreciably different on two consecutive days. The Linn et al. (1984c) and Sheppard et al. (1983) studies had several methodological differences; respectively, these were free breathing vs. mouthpiece, exercise vs. eucapnic hyperpnea, 4.5 h vs. 30 min interexposure interval, 5 min vs. 3 min exposure duration, and 0.6 ppm vs. 0.5 ppm SO_2 concentration. Nevertheless, in each study, an initial SO_2 exposure which produced at least a doubling of SRaw was followed later by a second exposure. With the shorter 30-min interval in the Sheppard study, the response to SO_2 was blunted. However, with the longer 5-h interval in the Linn study, the SO_2 response was unchanged from the initial exposure. Evidence from the exercise-induced bronchoconstriction literature (Edmunds et al., 1978; Stearns et al., 1981) indicates that the refractory period following exercise induced bronchoconstriction persists for 2 to 4 h. The refractory period following SO_2-induced bronchoconstriction lasts at least 30 min but less than 5 h.

Snashall and Baldwin (1982) studied the effect of exposures to 8 ppm SO_2 repeated at 4 h and 24 h in 4 normal and 1 asthmatic subjects. Compared to the initial exposures, SO_2-induced bronchoconstriction was reduced 42 percent at 4 h while no difference was observed at 24 h.

In a more comprehensive examination of repeated exercise during continuous SO_2 exposure in a large subject population (n=28) exposed to 3 different SO_2 levels with repeated exercise, Roger et al. (1985) also observed attenuation of SO_2-induced bronchoconstriction. The subjects worked at a moderate workload ($\dot{V}_E$ = 42 L/min) and breathed freely (except for 2 min at the end of exercise periods 2 and 3). They were not selected for SO_2 sensitivity, were sensitive to methacholine challenge, and used no cromolyn or steroids. Each subject was exposed, on three different days, to three SO_2 concentrations (0.25, 0.50, and 1.0). During each exposure, the subject exercised three times for 10 min each separated by 15-min intervals between exercise bouts. SRaw was measured pre-exposure and following each exercise period. After the first exercise, SRaw increased significantly over that seen with clean air (48 percent), with exposure to both 0.5 (+93 percent) and 1.0 ppm SO_2 (+191 percent). With subsequent exercise bouts in both 0.5 and 1.0 ppm SO_2, the SRaw increased only about half as much (third exercise SRaw increase was 52 percent and 116 percent in 0.5 and 1.0 ppm, respectively). This attenuation of response was less than that seen by Sheppard et al. (1983). Nevertheless, there were several differences between the two studies (exposure duration 3 min vs. 10 min, inter-exposure interval 30 min vs. 15 min, mouthpiece eucapnic hyperpnea vs. free breathing exercise, SO_2 sensitive vs. methacholine sensitive selection criterion). The subjects in this study demonstrated a refractoriness to both exercise in clean air and to exercise in SO_2; the latter was of greater absolute magnitude in terms of less increase in SRaw but the relative reduction in response from first to last exercise periods was similar for repeated exercise in either clean air or SO_2.

A subset of 10 subjects from the Roger et al. (1985) study were further studied by Kehrl and coworkers (1986, in press). The subjects were selected for moderate SO_2 sensitivity (i.e., no subjects non-responsive to SO_2 were used and the most reactive subjects were not studied). In addition to the three 10-min exercise periods performed previously, these subjects exercised continuously for 30 min at the same exercise intensity ($\dot{V}_E$ = 41 L/min) in an environmental chamber (26°C, 70 percent RH) while exposed to 1.0 ppm SO_2. The SRaw data for the original intermittent exercise exposures were similar to those of the original larger subject group (SRaw: baseline 5.4, postexercise-1 14.7, postexercise-2 12.8, postexercise-3 11.1). After 30 min continuous exercise in 1.0 ppm SO_2, SRaw significantly increased from 5.2 to 17.3 cm $H_2O\cdot$sec. The SRaw change was not significantly different than that seen after the first 10 minute exercise period of the intermittent exercise exposure. This study demonstrated that SO_2-induced bronchoconstriction is elicited by 10-min exposures but a further 20 min of continuous exercise resulted in only a slightly greater increase in SRaw which did not attain statistical significance.

In order to examine the time course of recovery from SO_2-induced bronchoconstriction in asthmatics, Hackney et al. (1984) exposed 17 mild to moderate, nonsmoking, SO_2-sensitive asthmatics (not using cromolyn or steroid medication) to 0.75 ppm SO_2 for 3 h. A secondary objective of this study was to determine the usefulness of spirometric testing as an adjunct or alternative to plethysmography under such exposure conditions. The exposure consisted of 3 h in an environmental chamber with a 10-min exercise period ($\dot{V}_E$ = 45 L/min) at the beginning of the exposure followed by post-exercise and hourly SRaw measurements. SRaw was approximately quadrupled (+263 percent) after exercise, returned almost to baseline at one hour (+34 percent, not significant) and was unquestionably back to baseline after 2 h recovery. In an otherwise identical exposure sequence which included spirometric testing, the $FEV_{1.0}$ was significantly reduced (-20 percent) post-exercise. The correlation between the $FEV_{1.0}$ and SRaw changes was significant ($r = 0.60$) but accounted for considerably less than half the variance, indicating that the two measures did not track each other closely in all subjects. This study demonstrated that moderate SO_2/exercise-induced bronchoconstriction will be relieved during rest (over a 1 to 2 h period) even if a low-level SO_2 exposure is continued. Second the authors demonstrated that changes in $FEV_{1.0}$ are also useful indicators of SO_2 exposure in asthmatics, although it is not clear that significant changes in $FEV_{1.0}$ would occur with less severe exposure more typical of the ambient environment.

4.3.5 Exacerbation of the Responses of Asthmatics to SO_2 by Cold/Dry Air

It has been well established that both cold air and dry air can exacerbate bronchoconstriction in asthmatics (Deal et al., 1979a; Strauss et al., 1977). The precise mechanism(s) for the effect are not universally agreed upon (Anderson, 1985). Although direct convective cooling of the airway plays a minor role, the major avenue of heat loss is due to evaporation to humidify the inspired air. Evaporation of airway surface liquid may also lead to other changes discussed in section 4.4. The potential for evaporative cooling by inhaled air can be most readily appreciated from the determination of the absolute humidity of the inspired air. Absolute humidity (AH) expresses the water content of the air in mg/L (g/m^3). The lower the AH, the greater the potential for evaporative cooling. AH is listed, for each study, in Table 4. For reference, the AH of saturated air at 37°C (i.e. BTPS) is 44 mg/liter. Therefore, in order to bring inspired air at 0°C, AH = 1 mg/L to BTPS, the temperature of each liter of air must be increased to 37°C (0.011 kcal) and 43 mg of water must be evaporated (0.025 kcal) (calculated from the respiratory heat exchange equation of Deal et al., 1979b).

Sulfur dioxide exposure can occur during the winter months when the ambient air temperature is low, and consequently the water vapor content is reduced. Accordingly, Bethel and coworkers (1984) examined the separate and combined effects of sulfur dioxide and cold dry air in seven asthmatics (mild to moderate asthma) breathing via mouthpiece. In this study and the following study by Sheppard and coworkers (1984), a series of bronchoprovocation tests were used. The methods are as follows:

> The subjects breathed a test gas mixture for 3 min, then SRaw was determined every 30 s for 2 min. This cycle of 3 min exposure and 2 min SRaw testing was repeated until the desired response was achieved. The ventilatory bronchoprovocation test consisted of performing voluntary eucapnic hyperventilation at increasing ventilation levels (20, 30, 40, 50, 60, etc. L/min) while breathing a single test gas mixture. The SO_2 bronchoprovocation test consisted of breathing (eucapnic hyperventilation) at some fixed ventilation and gas temperature and humidity with successively doubling levels of sulfur dioxide (e.g. 0, 0.125, 0.25, 0.50, 1.0, 2.0 ppm SO_2) used as the stimulus.

Bethel's subjects performed ventilatory bronchoprovocation tests with both 0.50 ppm SO_2 in warm humid air and with no SO_2 in cold-dry air (-11°C, dew point -15°C) until an increase in SRaw was observed in order to determine the ventilation which caused "little or no bronchoconstriction" with either stimulus. At the selected ventilation, subjects breathed on a mouthpiece for 3 min one of the following mixtures: (1) warm-humid (23°C, dew point = 18.4°C) air, (2) warm humid air with 0.50 ppm SO_2, (3)cold dry air, (4) cold dry air with 0.50 ppm SO_2. Modest but non-significant increases in SRaw followed each of the first three conditions [(1) +3 percent, (2) +38 percent, (3) +18 percent]. However, the combination of 0.50 ppm SO_2 and cold dry air caused a striking increase in SRaw (from 6.94 to 22.35, or a 222 percent increase). In this study, the combined effect of breathing cold dry air and 0.50 ppm SO_2 via mouthpiece was clearly larger than the sum of the individual response to either SO_2 or cold dry air.

Sheppard and coworkers (1984) further explored the interaction of breathing cold dry air and SO_2 via mouthpiece in a group of 8 mild asthmatics. The purpose of the study was to determine the relative contributions of decreased air temperature (-20°C) and reduced water vapor content (0 percent RH). Using a ventilatory bronchoprovocation test with cold dry air, the highest ventilation which did not cause increased SRaw was determined. The study consisted of having the subjects perform eucapnic voluntary hyperpnea, at the selected ventilation, 6 consecutive times for 3 min at a time with 2 min intervals between efforts. This was done on four separate occasions (different days) ordered randomly. On one occasion, the subject breathed cold-dry air only; this did not cause an increase in SRaw. The three other tests consisted of SO_2 bronchoprovocation tests at the selected ventilation with successive doubling SO_2 concentrations (starting at 0.125 ppm), one with cold dry air, one with warm-dry (22°C, 0 percent RH) air, and one with warm-humid (22°C, 70 percent RH) air. The SO_2 concentration required to produce a doubling of baseline SRaw (PC100) was interpolated from the dose-response curve. The PC100 for cold dry air (0.51 ppm) and for warm dry air (0.60 ppm) were not significantly different but both were less than the PC100 for warm humid air (0.87 ppm). The PC100 measured in this study may not be a useful effects index because the response may be a function of the cumulative effect of all SO_2 concentrations breathed, as noted by the authors. In addition, the authors considered the possible mitigating effect of repeated exposure - tolerance, but the importance of this is unclear. Further studies were performed using a ventilatory bronchoprovocation test while breathing either 0.0, 0.1, or 0.25 ppm SO_2 in warm-dry air. From the ventilation-SRaw dose-response plots at each SO_2 concentration, the ventilation producing an 80 percent increase in SRaw (PV80) was determined. The PV80 at 0.0, 0.1, and 0.25 ppm SO_2 were 54.9, 51.1, and 49.3 L/min, respectively. The differences in PV80 between 0.1 or 0.25 and clean air (0.0 ppm) reportedly reached significance although it was not clear how these data were analyzed (presumably repeated measures analysis of variance). Regardless of whether or not the difference in PV80 between clean air and 0.1 and 0.25 ppm SO_2 was statistically significant, the magnitude of this difference is small and of no established or obvious clinical importance. Nevertheless, the first part of this study did confirm that breathing dry air and cold air potentiates sulfur dioxide-induced bronchoconstriction. This potentiation could be an additive effect since both cooling (convective and evaporative) and drying of the airway may act as direct bronchoconstrictive stimuli, per se (Sheppard et al., 1984). In addition, the drying of the upper airway also reduces the ability of the oropharynx to scrub SO_2 from the inhaled air and may also cause a concentrating effect of the remaining airway surface liquid (see Mechanism section).

Concurrent studies by Linn and coworkers (1984a) also were directed at the possible interaction of inhalation of sulfur dioxide and cold air. They studied a group of 24 mild to moderate SO_2-sensitive asthmatics. A preliminary study to determine the effects of humidity at cold ambient temperatures included eight subjects exposed to 0.0, 0.2, 0.4, and 0.6 ppm SO_2 at 5°C under two humidity conditions (81 percent and 54 percent). The subjects exercised for 5 min in an environmental chamber at a workload selected to elicit a ventilation of approximately 50 L/min (range 37 to 60) and breathed naturally. SRaw showed a tendency to increase more from pre- to post-exposure with increased SO_2 concentration. The post-hoc analyses for changes at each concentration were not presented, presumably because of the small sample size and the non-randomized experimental design. No effect of ambient humidity on response to SO_2 was seen at the 5°C air temperature. However, the difference in water vapor content at the low and high humidities was approximately 1.84 mg/L, approximately 1/20 of the difference in water vapor pressure between ambient and BTPS, and thus the absence of a difference should have been expected. A second study in this same series compared responses of 24 asthmatic subjects exposed to 0.6 ppm SO_2 under warm-humid (22°C, 85 percent RH, AH = 16.5) and cold humid (5°C, 85 percent RH, AH = 3.4) conditions. The same exercise and natural breathing procedures as above were followed. Breathing 0.0 ppm SO_2, subjects had small non-significant increases in SRaw under warm (27 percent) and cold (38 percent) conditions. 0.6 ppm SO_2 exposure under these temperature-humidity conditions produced significant increases in SRaw in both warm (132 percent) and cold (182 percent) conditions. However, the temperature effect, unlike in the Sheppard et al. (1984) and Bethel et al. (1984) studies, was not significant although the trend was in the direction of an increased response at the lower temperature. The temperature difference between cold and warm air was larger in the Sheppard et al. and Bethel et al. studies (42°C and 34°C, respectively) compared to the Linn et al. study (17°C). However the cold-warm difference in inspired air water content (AH) were similar for the three studies (14.8, 12.6, 13.1 respectively). Nevertheless, it is apparent that the exacerbation of SO_2-induced bronchoconstriction by cold air, containing small quantities of water vapor, is minimal in freely breathing asthmatics exposed during moderately heavy exercise at 5°C air temperature.

In order to determine the possible effects of even colder ambient air temperatures, Linn et al. (1984b) exposed 24 mild SO_2-sensitive asthmatics (including 11 subjects from Linn, 1984a) to 0.0, 0.3, and 0.6 ppm SO_2 at +21,

+7, and -6°C (RH approximately 78 percent). The exposure duration was 5 min. The authors noted that "only 10-20 percent of clinically asthmatic prospective subjects had to be rejected as non-responsive to SO_2" (10 min exercise at 40 L/min breathing 0.75 ppm SO_2). There was a significant effect of decreasing air temperature and of increasing SO_2 concentration on the post-exercise SRaw. However, the authors reported that there was no statistically significant interaction of air temperature and SO_2 concentration for SRaw although the interaction was apparently significant for SGaw. The effect of cold air (in increasing SRaw or decreasing SGaw) was most pronounced with the 0.0 ppm SO_2 exposures and minimal with 0.6 ppm exposures. The results of this study do not support the hypothesis that SO_2 acts synergistically with cold air in freely breathing, exercising, mild to moderate asthmatics. The authors concluded that the cold air and SO_2 effects "acted additively at most." The results for the 7°C and 21°C 0.6 ppm SO_2 exposures (+207 percent, +150 percent SRaw) were similar to those seen in their previous (1984a) study (+182 percent, +132 percent SRaw), thus demonstrating the reproducibility of these studies.

In order to study the full range of SO_2-temperature-humidity interactions, Linn et al. (1985a) also examined the effects of warm-dry (38°C, 20 percent RH) and warm-humid (38°C, 85 percent RH) conditions on 22 SO_2-exposed (0.6 ppm) asthmatics. The exposure protocol was similar to the two 1984 studies with a 5 min chamber exercise period and ventilation of approximately 50 L/min. The experimental design was a three-factor (SO_2-0.0 and 0.6 ppm; temperature-21 and 38°C; and humidity-20 percent and 80 percent) factorial design with repeated measures across all factors. In this study, the major differences would be anticipated to occur between the warm humid (38°C, 85 percent RH) condition and the cooler dryer condition (21°C, 20 percent RH). There were significant effects of temperature, SO_2 and humidity on the delta-SRaw (pre to post-exercise) response and significant temperature-SO_2 and humidity-SO_2 interactions. The largest clean air increase in SRaw (20 percent) occurred with cool-dry air and the smallest with warm-humid. The largest SO_2 induced increase in SRaw (204 percent) occurred under cool-dry conditions and again the smallest change (35 percent) occurred under warm-humid conditions. Symptoms showed a similar pattern of response after SO_2 exposures with lower symptoms scores under warm-humid than cool-dry conditions. SRaw responses to 0.6 ppm SO_2 under 21°C-humid conditions were similar for all three Linn et al. studies (1984a, 132 percent; 1984b, 150 percent; 1985a, 157 percent). The response under warm humid conditions was considerably less. The authors discussed the possibility that they observed a synergism between SO_2 exposure and airway drying/cooling due to reduced temperature or humidity of inspired air.

4.4 MECHANISM(S)

4.4.1 Mode of Action

A single unequivocal definition of asthma is not realistic on the basis of existing knowledge and the heterogeneity of the disease. The single condition that is common to all definitions of asthma is the reversibility of slowed forced expiration presumably due to airway narrowing (smooth muscle contraction, excess mucous secretion, mucosal edema). Most current definitions of asthma also include the concept of nonspecific airway hyperreactivity (e.g., methacholine, histamine). The present American Thoracic Society definition of asthma is:

> A disease characterized by an increased responsiveness of the airways to various stimuli and manifested by slowing of forced expiration which changes in severity either spontaneously or with treatment.

It is noteworthy that the data summarized in this addendum indicate that asthmatics experience substantial, but transient, bronchoconstriction (slowed forced expiration) when exposed to low SO_2 concentrations (i.e. increased responsiveness).

Because of its relatively rapid reversibility, SO_2-induced bronchoconstriction in asthmatics is likely the result of decreased airway caliber caused by contraction of airway smooth muscle. The study of Roger et al. (1985) indicated the largest SO_2-induced increases in airway resistance measured by plethysmography were associated with increases in the low frequency component of respiratory system impedance measured by the forced random oscillation (noise) technique. The interpretation of this finding was an elevated peripheral resistance associated with constriction of anatomically peripheral or small airways. However, narrowing of central upper airway structures such as the larynx and glottis may accompany increased airway resistance (Cole, 1982) and it is possible that some of the increase in airway resistance may be due to elevated laryngeal or glottal resistance.

Contraction of airway smooth muscle in response to environmental stimuli can be evoked by intrinsic chemical and/or physical stimuli acting via neural and/or humoral pathways. SO_2 may either act directly on smooth muscle or may cause the release of chemical mediators from tissue, especially the release of histamine from mast cells. It is beyond the scope of this document to provide even a brief review of the mechanism of action of all the possible pharmacologic mediators of SO_2-induced bronchoconstriction. However, some plausible candidates include histamine, slow-reacting substance of anaphylaxis, leukotrienes, and prostaglandin F_2-alpha, all of which are released in the airways and can cause smooth muscle contraction.

As reported in the previous addendum (U.S. EPA, 1982c), both activation of parasympathetically mediated reflexes (Nadel et al., 1965; Sheppard et al., 1980) and mast cell degranulation (Sheppard et al., 1981) with consequent release of chemical mediator (most likely histamine) play a significant role in SO_2-induced bronchoconstriction. While the specific mechanism whereby SO_2 interacts with the airways to induce bronchoconstriction has not been elucidated, two reports of studies relevant to the mechanism(s) have appeared since the previous addendum. These studies assessed the inhibitory effects on SO_2-induced bronchoconstriction of a variety of receptor antagonists (drugs that bind the receptors but do not stimulate the receptor-induced response). Results from these studies suggest that mechanisms in addition to reflex bronchoconstriction and mast cell degranulation may play a significant part in the responses of the asthmatic airway to SO_2.

Snashall and Baldwin (1982) studied the effects of atropine and cromolyn on relatively mild bronchoconstriction (Raw increased <100 percent above baseline) induced by breathing 8 ppm SO_2 at rest. Both atropine and cromolyn at least partially blocked SO_2-induced bronchoconstriction in all but one of 11 normal subjects. The degree of atropine blockade was inversely related to the magnitude of the SO_2-induced response ($r = -0.75$), i.e., small responses were completely blocked, while there was little blockade of large responses. For asthmatics, atropine enhanced SO_2-induced bronchoconstriction in three of four subjects tested; minimal blockade was observed in the remaining subject. Cromolyn blocked the SO_2-induced response in three of the four asthmatic subjects.

Tan et al. (1982) exposed resting normal and atopic subjects to 20 ppm and asthmatics to 10 ppm SO_2 to induce bronchoconstriction. Both ipratropium bromide (IB, an anticholinergic agent similar to atropine) and cromolyn partially inhibited the SO_2-induced response in all normal and atopic subjects tested. For asthmatics, IB had little effect on SO_2-induced bronchoconstriction in five of nine subjects and afforded only partial blockade in the remaining four subjects. Cromolyn at least partially inhibited SO_2-induced bronchoconstriction in all 18 asthmatics tested. Clemastine (a selective H_1 receptor antagonist without anticholinergic or antiserotinergic activity) effectively blocked the SO_2-induced response in five of seven asthmatic subjects tested.

4.4.2 Breathing Mode and Interaction With Dry Air

There is no question that the magnitude of SO_2-induced bronchoconstriction is significantly greater with oral than with oronasal or nasal breathing (Kirkpatrick et al., 1982). When SO_2 is inhaled by mouth more SO_2 penetrates beyond the pharynx to sites involved in the induction of bronchoconstriction (Bethel et al., 1983b; Kleinman, 1984). It is assumed that because of their geometry and greater relative surface area, the nasal passages are capable of effectively removing most SO_2 breathed at rest and a large percentage during conditions of increased ventilation (exercise, isocapnic hyperpnea). While there is certainly less relative surface area available for SO_2 scrubbing in the oral cavity, other factors may also influence increased bronchoconstriction associated with mouth breathing of SO_2, especially at higher ventilation rates.

Increased oral ventilation may result in substantial drying of both upper (oral and pharyngeal area) and lower (larynx and trachea) airways. The extent of airway surface drying will depend upon the ventilation (air flow rate) and water content of inhaled air. Airway drying could lead to alterations in both the quantity and properties of surface liquid in the airways. Decreased volume of and/or surface area of liquid in the upper airway may result in decreased efficiency of SO_2 absorption, allowing deeper penetration of the gas to sites in the intrathoracic airway more likely involved in the induction of bronchoconstriction. Decreased quantity of surface liquid in the lower airway may result in a reduced volume in which soluble gases such as SO_2 can form solutions. The chemical interactions of SO_2 and SO_2-generated ionic species could be altered by reduced fluid volume or by changes in concentrations of other substances in surface liquid, which could alter the equilibria between the SO_2 ionic species. Another factor which is altered by drying of airway surface liquid is its osmolarity. Hyperosmolar solutions can induce bronchoconstriction (Anderson, 1985) and could be associated with enhancement of SO_2-induced bronchoconstriction.

Two laboratories (Cardiovascular Research Institute, UCSF, and Rancho Los Amigos Hospital) have performed the bulk of the work on the interaction of SO_2

breathing and inhaled air temperature and humidity. Although the results of the two labs have been qualitatively similar, the mouthpiece breathing studies (e.g. Bethel et al., 1983b) have typically yielded more pronounced increases in airway resistance. In SO_2 exposures using oronasal ventilation, interlaboratory differences have been smaller. The use of mouthpiece breathing results in a more direct airflow path of lower resistance than does unencumbered oronasal breathing (Proctor, 1981; Cole, 1982). Under situations of unencumbered oronasal breathing, the mouth may act as an effective organ of air modification (i.e. warming, humidifying, scrubbing of particles and soluble gases). During mouthpiece breathing, this effectiveness is reduced because of the alteration in oral airway geometry. Thus some of the difference between laboratories may be due to differences in the amount of airway drying and the volume of nasal ventilation, both of which would favor greater upper airway SO_2 scrubbing in studies using oronasal ventilation. Undoubtedly subject selection criteria and medication also play an important role in the magnitude of response but such differences between study series are not obvious (see subject table). Another possibility, noted incidentally by Koenig et al. (1985), is that subjects may deliberately breathe via the nasal airway, despite the higher resistance, in order to alleviate both the drying effect due to cold (and/or dry) air and the effect of SO_2 which may be associated with the distinctive odor or taste.

Cole (1982) notes that approximately 85 percent of adults are preferential nose breathers who only resort to oral or oronasal breathing under the demanding conditions of exercise, nasal obstruction, or speech. This occurs despite the fact that upper airway resistance via the nasal airway is about twice that via a mouthpiece. However, Bethel et al. (1983b) suggest more asthmatics may breath oronasally and that asthmatics switch from nasal to oronasal breathing at a lower ventilation than normals; this is due to the greater prevalence of rhinitis in the asthmatic population.

4.4.3 Tolerance (Attenuation of Response) to SO_2 With Repeated Exposure

Attenuation of SO_2-induced bronchoconstriction with repeated SO_2 exposure (with eucapnic hyperpnea) was not associated with a decrease in airway responsiveness to histamine (Sheppard et al., 1983). This indicates that this attenuation of response was not related to decreased responsiveness of airway smooth muscle or decreased responsiveness of vagal reflex pathways. These authors did suggest that depletion of mediators or a selective inhibition of SO_2-sensitive afferents might be involved in this phenomenon. For equivalent total exercise time, Kehrl et al. (1986) observed greater SO_2-induced bronchoconstriction with continuous as compared to intermittent exercise during SO_2 exposure. These findings suggest that mediator depletion or selective inhibition of afferents, as well as exercise-induced release of endogenous bronchodilators (epinephrine) are probably not related to the attenuation of response with repeated exposure (or repeated intermittent exercise during exposure).

The results obtained by Kehrl et al. (1986) are highly suggestive that the attenuation of SO_2-induced bronchoconstriction is related to events that occur during the post-exposure/post-exercise recovery periods rather than events occurring during the exposure per se. It is likely that during the recovery periods, there is some mechanism that first helps alleviate bronchoconstriction and may then prepare the subject for subsequent challenge. Without the recovery period, the continuing stimuli of high ventilatory rates and SO_2 exposure overwhelm any attenuating process resulting in unremitting or increasing bronchoconstriction. Since drying of the upper airways with resultant changes in surface liquid quantities and properties has been strongly implicated in the positive interactions between ventilation and SO_2 exposure, perhaps a corollary mechanism may account for the attenuation of SO_2-induced response.

It is clear that increased evaporation of water from airway mucosal surfaces must occur during exercise or hyperventilation (Anderson, 1985). The continuance of increased production and/or secretion of airway surface liquid during recovery periods may result in decreased delivery of SO_2 during subsequent inhalation of SO_2. Whether or not SO_2 has any effect on surface liquid quantity is unknown. Increased liquid in the lower airways would prevent severe alterations in surface liquid properties postulated to occur when SO_2 is dissolved in this liquid. Protection from subsequent challenges would be a time-dependent phenomenon and would resolve as the factors governing airway surface liquid homeostasis gradually return to normal.

Attenuation of bronchoconstriction has been reported for exercise (Stearns et al., 1981) and hyperpnea of cold, dry air (Bar-Yishay et al. 1983, Wilson et al., 1982) repeated at short time intervals, suggesting that the attenuation of SO_2-induced bronchoconstriction may be secondary to this decline in response.

4.5 CONCLUSIONS

Studies which have been published in the scientific literature since 1982 support many of the conclusions reached in the criteria document and the previous addendum.

The new studies clearly demonstrate that asthmatics are much more sensitive to SO_2 as a group. Nevertheless, it is clear that there is a broad range of sensitivity to SO_2 among asthmatics exposed under similar conditions. Recent studies also confirm that normal healthy subjects, even with moderate to heavy exercise, do not experience effects on pulmonary function due to SO_2 exposure in the range of 0 to 2 ppm. The minor exception may be the annoyance of the unpleasant smell or taste associated with SO_2. The suggestion that asthmatics are about an order of magnitude more sensitive than normals is thus confirmed.

There is no longer any question that normally breathing asthmatics performing moderate to heavy exercise will experience SO_2-induced bronchoconstriction when breathing SO_2 for at least 5 min at concentrations less than 1 ppm. Durations beyond 10 min do not appear to cause substantial worsening of the effect. The lowest concentration at which bronchoconstriction is clearly worsened by SO_2 breathing depends on a variety of factors.

Exposure to less than 0.25 ppm has not evoked group mean changes in responses. Although some individuals may appear to respond to SO_2 concentrations less than 0.25 ppm, the frequency of these responses is not demonstrably greater than with clean air. Thus individual responses cannot be relied upon for response estimates, even in the most reactive segment of the population.

In the SO_2 concentration range from 0.2 to 0.3 ppm, six chamber exposure studies were performed with asthmatics performing moderate to heavy exercise. The evidence that SO_2-induced bronchoconstriction occurred at this concentration with natural breathing under a range of ambient conditions was equivocal. Only with oral mouthpiece breathing of dry air (an unusual breathing mode under exceptional ambient conditions) were small effects observed on a test of questionable quantitative relevance for criteria development purposes. These findings are in accord with the observation that the most reactive subject in the Horstman et al. (1986) study had a $PCSO_2$ (SO_2 concentration required to double SRaw) of 0.28 ppm.

Several observations of significant group mean changes in SRaw have recently been reported for asthmatics exposed to 0.4 to 0.6 ppm SO_2. Most if not all studies, using moderate to heavy exercise levels (>40 to 50 L/min), found evidence of bronchoconstriction at 0.5 ppm. At a lower exercise rate, other studies (e.g., Schachter et al., 1984) did not produce clear evidence of SO_2-induced bronchoconstriction at 0.5 ppm SO_2. Exposures which included higher ventilations, mouthpiece breathing, and inspired air with a low water content resulted in the greatest responses. Mean responses ranged from 45 percent (Roger et al., 1985) to 280 percent (Bethel et al., 1983b) increase in SRaw. At concentrations in the range of 0.6 to 1.0 ppm, marked increases in SRaw are observed following exposure. Recovery is generally complete within approximately 1 h although the recovery period may be longer for subjects with the most severe responses.

It is now evident that for SO_2-induced bronchoconstriction to occur in asthmatics at concentrations less than 0.75 ppm, the exposure must be accompanied by hyperpnea. Ventilations in the range of 40 to 60 L/min have been most successful; such ventilations are beyond the usual oronasal ventilatory switchpoint.

There is no longer any question that oral breathing (especially via mouthpiece) causes exacerbation of SO_2-induced bronchoconstriction. New studies reinforce the concept that the mode of breathing is an important determinant of the intensity of SO_2-induced bronchoconstriction in the following order: oral > oronasal > nasal.

A second exacerbating factor strongly implicated in recent reports is the breathing of dry and/or cold air with SO_2. It has been suggested that the reduced water content and not cold, per se, could be responsible for much of this effect. Airway drying may contribute to the SO_2 effect by decreasing the efficacy of SO_2 scrubbing by the surface liquid of the oral and nasal airway. Drying of airways peripheral to the laryngopharynx may result in decreased surface liquid volume to buffer the effects of SO_2.

The new studies do not provide sufficient additional information to establish whether the intensity of the SO_2-induced bronchoconstriction depends upon the severity of the disease. Across a broad clinical range from "normal" to moderate asthmatic there is clearly a relationship between the presence of asthma and sensitivity to SO_2. Within the asthmatic population, the relationship of SO_2 sensitivity to the qualitative clinical severity of asthma has not been studied systematically. Ethical considerations (i.e., continuation of appropriate medical treatment) prevent the unmedicated exposure of the "severe" asthmatic because of his dependence upon drugs for control of his asthma. True determination of sensitivity requires that the interference with SO_2 response caused by such medication be removed. Because of these mutually exclusive requirements, it is unlikely that the true SO_2 sensitivity of severe asthmatics will be determined. Nevertheless, more severe asthmatics should be studied. Alternative methods to those used with mild asthmatics, not critically dependant on regular medication, will be required. The studies to date have only addressed the "mild to moderate" asthmatic.

Consecutive SO_2 exposures (repeated within 30 min or less) result in a diminished response compared with the initial exposure. It is apparent that this refractory period lasts at least 30 min but that normal reactivity returns within 5 h. The mechanisms and time course of this effect are not clearly established but refractoriness does not appear to be related to an overall decrease in bronchomotor responsiveness.

From the review of studies included in this addendum, it is clear that the magnitude of response (typically bronchoconstriction) induced by any given SO_2 concentration was variable among individual asthmatics. Exposures to SO_2 concentrations of 0.25 ppm or less, which did not induce significant group mean increases in airway resistance also did not cause symptomatic bronchoconstriction in individual asthmatics. On the other hand, exposures to 0.40 ppm SO_2 or greater (combined with moderate to heavy exercise) which induced significant group mean increases in airway resistance,also caused substantial bronchoconstriction in some invididual asthmatics. This bronchoconstriction was associated with wheezing and the perception of respiratory distress. In several instances it was necessary to discontinue the exposure and provide medication. The significance of these observations is that some SO_2-sensitive asthmatics are at risk of experiencing clinically significant (i.e., symptomatic) bronchoconstriction requiring termination of activity and/or medical intervention when exposed to SO_2 concentrations of 0.40 ppm or greater when this exposure is accompanied by at least moderate activity.

CHAPTER 5. EXECUTIVE SUMMARY

In general, studies published in the scientific literature since 1981-82 support many of the conclusions reached in the earlier criteria review (U.S. EPA, 1982a,c). Some of the key findings emerging from the present evaluation of the newly available information on health effects associated with exposure to PM and SO_x are summarized here.

5.1 RESPIRATORY TRACT DEPOSITION AND FATE

Studies published since preparation of the earlier criteria document (U.S. EPA, 1982a) and the previous addendum (U.S. EPA, 1982c) support the conclusions reached at that time and provide clarification of several issues. In light of previously available data, new literature was reviewed with a focus towards (1) the thoracic deposition and clearance of large particles, (2) assessment of deposition during oronasal breathing, (3) deposition in possibly susceptible subpopulations, such as children, and (4) information that would relate the data to refinement or interpretation of ancillary issues, such as inter- and intrasubject variability in deposition, deposition of monodisperse versus polydisperse aerosols, etc.

The thoracic deposition of particles ≥ 10 µm D_{ae} and their distribution in the TB and P regions has been studied by a number of investigators (Svartengren, 1986; Heyder, 1986; Emmett et al., 1982). Depending upon the breathing regimen used, TB deposition ranged from 0.14 to 0.36 for 10-µm D_{ae} particles, while the range for 12-µm D_{ae} particles was 0.09 to 0.27. For particles 16.4 µm D_{ae}, a maximally deep inhalation pattern resulted in TB deposition of 0.12. While the magnitude of deposition in various regions depends heavily upon minute ventilation, there is, in general, a gradual decline in thoracic deposition for large particle sizes, and there can be significant deposition of particles greater than 10 µm D_{ae}, particularly for individuals who habitually breathe through their mouth. Thus, the deposition experiments wherein subjects inhale through a mouthpiece are relevant to examining the potential of particles to penetrate to the lower respiratory tract and pose a potentially increased risk. Increased risk may be due to increased localized dose or to the exceedingly long half-times for clearance of larger particles (Gerrity et al., 1983).

Although experimental data are not currently available for deposition of particles in the lungs of children, some trends are evident from the modeling results of Phalen et al. (1985). Phalen and co-workers made morphometric measurements in replica lung casts of people aged 11 days to 21 years and modeled deposition during inspiration as a function of activity level. They found that, in general, increasing age is associated with decreasing particulate deposition efficiency. However, very high flow rates and large particulate sizes do not exhibit consistent age-dependent differences. Since minute ventilation at a given state of activity is approximately linearly related to body mass, children receive a higher TB dose of particles than do adults and would appear to be at a greater risk, other factors (i.e., mucociliary clearance, particulate losses in the head, tissue sensitivity, etc.) being equal.

5.2 SUMMARY OF EPIDEMIOLOGIC FINDINGS ON HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO AIRBORNE PARTICLES AND SO_x

Newly available reanalyses of data relating mortality in London to short-term (24-h) exposures to PM (measured as smoke) and SO_2 were evaluated and their results compared with earlier findings and conclusions discussed in U.S. EPA (1982a). Varying strengths and weaknesses were evident in relation to the different individual reanalyses evaluated and certain questions remain unresolved concerning most. Regardless of the above considerations, the following conclusions appear warranted based on the earlier criteria review (U.S. EPA, 1982a) and present evaluation of newly available analyses of the London mortality experience: (1) markedly increased mortality occurred, mainly among the elderly and chronically ill, in association with BS and SO_2 concentrations above 1000 $\mu g/m^3$, especially during episodes when such pollutant elevations occurred for several consecutive days; (2) the relative contributions of BS and SO_2 cannot be clearly distinguished from those of each other, nor can the effects of other factors be clearly delineated, although it appears likely that coincident high humidity (fog) was also important (possibly in providing conditions leading to formation of H_2SO_4 or other acidic aerosols); (3) increased risk of mortality is associated with exposure to BS and SO_2 levels in the range of 500 to 1000 μg/m^3, clearly at concentrations in excess of ~700 to 750 μg/m^3; and (4) less certain evidence suggests possible slight increases in the risk of mortality at BS levels below 500 μg/m^3, with no specific threshold levels having yet been demonstrated or ruled out at lower concentrations of BS (e.g., at 150 μg/m^3) nor potential contribution of other plausibly confounding variables having yet been fully evaluated.

In addition to the reanalyses of London mortality data, reanalyses of mortality data from New York City in relation to air pollution reported by Ozkaynak and Spengler (1985) were evaluated. Time-series analyses were carried out on a subset of New York City data included in a prior analysis by Schimmel (1978) which was critiqued during the earlier criteria review (U.S. EPA, 1982a). The reanalyses by Ozkaynak and Spengler (1985) evaluated 14 years (1963-76) of daily measurements of mortality (the sum of heart, other circulatory, respiratory, and cancer mortality), COH, SO_2, and temperature. In summary, the newly available reanalyses of New York City data raise possibilities that, with additional work, further insights may emerge regarding mortality-air pollution relationships in a large U.S. urban area. However, the interim results reported thus far do not now permit definitive determination of their usefulness for defining exposure-effect relationships, given the above-noted types of caveats and limitations.

Similarly, it is presently difficult to accept findings reported in another new study of mortality associated with relatively low levels of SO_2 pollution in Athens, given questions regarding representativeness of the monitoring data and the statistical soundness of using deviations of mortality from an earlier baseline relatively distant in time. Lastly, a newly reported analyses of mortality-air pollution relationships in Pittsburgh (Allegheny County, PA) was evaluated as having utilized inadequate exposure characterization and the results contain sufficient internal inconsistencies, so that the analyses are not useful for delineating mortality relationships with either SO_2 or PM.

Of the newly-reported analyses of short-term PM/SO_x exposure-morbidity relationships discussed in this Addendum, the Dockery et al. (1982) study provides the best-substantiated and most readily interpretable results. Those results, specifically, point toward decrements in lung function occurring in association with acute, short-term increases in PM and SO_2 air pollution. The small, reversible decrements appear to persist for 1-2 wks after episodic exposures to these pollutants across a wide range, with no clear delineation of threshold yet being evident. In some study periods effects may have been due to TSP and SO_2 levels ranging up to 422 and 455 $\mu g/m^3$, respectively. Notably larger decrements in lung function were discernable for a subset of children (responders) than for others. The precise medical significance of the observed decrements per se or any consequent long-term sequalae remain to be determined. The nature and magnitude of lung function decrements found by Dockery et al. (1982), it should be noted, are also consistent with: observations of Stebbings and Fogelman (1979) of gradual recovery in lung function of children during seven days following a high PM episode in Pittsburgh, PA (max 1-hr TSP estimated at 700 $\mu g/m^3$); and a report by Saric et al. (1981) of 5 percent average declines in $FEV_{1.0}$ being associated with high SO_2 days (89-235 $\mu g/m^3$).

In regard to evaluation of long-term exposure effects, the 1982 U.S. EPA criteria document (1982a) noted that certain large-scale "macroepidemiological" (or "ecologic" studies as termed by some) have attracted attention on the basis of reported demonstrations of associations between mortality and various indices of air pollution, e.g., PM or SO_x levels. U.S. EPA (1982a) also noted that various criticisms of then-available ecologic studies made it impossible to ascertain which findings may be more valid than others. Thus, although many of the studies qualitatively suggested positive associations between mortality and chronic exposure to certain air pollutants in the United States, many key issues remained unresolved concerning reported associations and whether they were causal or not.

Since preparation of the earlier Criteria Document (U.S. EPA, 1982a) additional ecological analyses have been reported regarding efforts to assess relationships between mortality and long-term exposure to particulate matter and other air pollutants. For example, Lipfert (1984) conducted a series of cross-sectional multiple regression analyses of 1969 and 1970 mortality rates for up to 112 U.S. SMSA's, using the same basic data set as Lave and Seskin (1978) for 1969 and taking into account various demographic, environmental and lifestyle variables (e.g., socioeconomic status and smoking). Also, the Lipfert (1984) reanalysis included several additional independent variables: diet; drinking water variables; use of residential heating fuels; migration; and SMSA growth. New dependent variables included age-specific mortality rates with their accompanying sex-specific age variables. Both linear and several nonlinear (e.g., quadratic or linear splines testing for possible threshold model specifications) were evaluated.

It became quite evident from the results obtained that the air pollution regression results for the U.S. data sets analyzed by Lipfert (1984) are extremely sensitive to variations in the inclusion/exclusion of specific observations (for central city versus SMSA's or different subsets of locations) or additional explanatory variables beyond those used in the earlier Lave and Seskin analyses. The results are also highly dependent upon the particular model specifications used, i.e. air pollution coefficients vary in strength of association with total or age-/sex-specific mortality depending upon the form of the specification and the range of explanatory variables included in the analyses. Lipfert's overall conclusion was that the sulfate regression coefficients are not credible and, since sulfate and TSP interact with each other in these regressions, caution is warranted for TSP coefficients as well.

Ozkaynak and Spengler (1985) have also newly described results from ongoing attempts to improve upon previous analyses of mortality and morbidity effects of air pollution in the United States. Ozkaynak and Spengler (1985) present principal findings from a cross-sectional analysis of the 1980 U.S. vital statistics and available air pollution data bases for sulfates, and fine, inhalable and total suspended particles. In these analyses, using multiple regression methods, the association between various particle measures and 1980 total mortality were estimated for 98 and 38 SMSA subsets by incorporating recent information on particle size relationships and a set of socioeconomic variables to control for potential confounding. Issues of model misspecification and spatial autocorrelation of the residuals were also investigated.

The Ozkaynak and Spengler (1985) results for 1980 U.S. mortality provide an interesting overall contrast to the findings of Lipfert (1984) for 1969-70 U.S. mortality data. Whereas Lipfert found TSP coefficients to be most consistently statistically significant (although varying widely depending upon model specifications, explanatory variables included, etc.), Ozkaynak and Spengler found particle mass measures including coarse particles (TSP, IP) often to be non-significant predictors of total mortality. Also, whereas Lipfert found the sulfate coefficients to be even more unstable than the TSP associations with mortality (and questioned the credibility of the sulfate coefficients), Ozkaynak and Spengler found that particle exposure measures related to the respirable or toxic fraction of the aerosols (e.g., FP or sulfates) to be most consistently and significantly associated with annual cross-sectional mortality rates. It might be tempting to hypothesize that changes in air quality or other factors from the earlier data sets (for 1969-70) analyzed by Lipfert (1984) to the later data (for 1980) analyzed by Ozkaynak and Spengler (1985, 1986) may at least partly explain their contrasting results, but there is at present no basis by which to determine if this is the case or which set of findings may or may not most accurately characterize associations between mortality and chronic PM or SO_x exposures in the United States. Thus conclusions stated in U.S EPA (1982a) concerning ecologic analyses still largely apply here in regard to mortality PM/SO_x relationships.

The present Addendum also evaluated a growing body of new literature on morbidity effects associated with chronic exposures to airborne particles and sulfur oxides. In summary, of the numerous new studies published on morbidity effects associated with long-term exposures to PM or SO_x, only a few may provide potentially useful results by which to derive quantitative conclusions concerning exposure-effect relationships for the subject pollutants. A study by Ware et al. (1986), for example, provides evidence of respiratory symptoms in children being associated with particulate matter exposures in contemporary U.S. cities without evident threshold across a range of TSP levels of ~25 to 150 $\mu g/m^3$. The increase in symptoms appears to occur without concomitant decrements in lung function among the same children. The medical significance the observed increased in symptoms unaccompanied by decrements in lung of function remains to be fully evaluated but is of likely health concern. Caution is warranted, however, in using these findings for risk assessment purposes in view of the lack of significant associations for the same variables when assessed from data within individual cities included in the Ware et al. (1985) study.

Other new American studies provide evidence for: (1) increased respiratory symptoms among young adults in association with annual-average SO_2 levels of ~115 $\mu g/m^3$ (Chapman et al., 1983); and (2) increased prevalence of cough in children (but not lung function changes) being associated with intermittent exposures to mean peak 3-hr SO_2 levels of ~1.0 ppm or annual average SO_2 levels of ~103 $\mu g/m^3$ (Dodge et al., 1985).

Results from one European study (PAARC, 1982a,b) also suggest the likelihood of lower respiratory disease symptoms and decrements in lung function in adults (both male and female) being associated with annual average SO_2 levels ranging without evident threshold from about 25 to 130 μg/m^3. In addition that study suggests that upper respiratory disease and lung function decrements in children may also be associated with annual-average SO_2 levels across the above range. Further analyses would probably be necessary to determine whether or not any thresholds for the health effects reported by PAARC (1982a,b) exist within the stated range of annual-average SO_2 values.

5.3 SUMMARY OF CONTROLLED HUMAN EXPOSURE STUDIES OF SULFUR DIOXIDE HEALTH EFFECTS

The new studies clearly demonstrate that asthmatics are much more sensitive to SO_2 as a group. Nevertheless, it is clear that there is a broad range of sensitivity to SO_2 among asthmatics exposed under similar conditions. Recent studies also confirm that normal healthy subjects, even with moderate to heavy exercise, do not experience effects on pulmonary function due to SO_2 exposure in the range of 0 to 2 ppm. The minor exception may be the annoyance of the unpleasant smell or taste associated with SO_2. The suggestion that asthmatics are about an order of magnitude more sensitive than normals is thus confirmed.

There is no longer any question that normally breathing asthmatics performing moderate to heavy exercise will experience SO_2-induced bronchoconstriction when breathing SO_2 for at least 5 min at concentrations less than 1 ppm. Durations beyond 10 min do not appear to cause substantial worsening of the effect. The lowest concentration at which bronchoconstriction is clearly worsened by SO_2 breathing depends on a variety of factors.

Exposure to less than 0.25 ppm has not evoked group mean changes in responses. Although some individuals may appear to respond to SO_2 concentrations less than 0.25 ppm, the frequency of these responses is not demonstrably greater than with clean air. Thus individual responses cannot be relied upon for response estimates, even in the most reactive segment of the population.

In the SO_2 concentration range from 0.2 to 0.3 ppm, six chamber exposure studies were performed with asthmatics performing moderate to heavy exercise. The evidence that SO_2-induced bronchoconstriction occurred at this concentration with natural breathing under a range of ambient conditions was equivocal. Only with oral mouthpiece breathing of dry air (an unusual breathing mode under exceptional ambient conditions) were small effects observed on a test of questionable quantitative relevance for criteria development purposes. These findings are in accord with the observation that the most reactive subject in the Horstman et al. (1986) study had a $PCSO_2$ (SO_2 concentration required to double SRaw) of 0.28 ppm.

Several observations of significant group mean changes in SRaw have recently been reported for asthmatics exposed to 0.4 to 0.6 ppm SO_2. Most if not all studies, using moderate to heavy exercise levels (>40 to 50 L/min), found evidence of bronchoconstriction at 0.5 ppm. At a lower exercise rate, other studies (e.g., Schachter et al., 1984) did not produce clear evidence of SO_2-induced bronchoconstriction at 0.5 ppm SO_2. Exposures which included higher ventilations, mouthpiece breathing, and inspired air with a low water content resulted in the greatest responses. Mean responses ranged from 45 percent (Roger et al., 1985) to 280 percent (Bethel et al., 1983b) increase in SRaw. At concentrations in the range of 0.6 to 1.0 ppm, marked increases in SRaw are observed following exposure. Recovery is generally complete within approximately 1 h although the recovery period may be longer for subjects with the most severe responses.

It is now evident that for SO_2-induced bronchoconstriction to occur in asthmatics at concentrations less than 0.75 ppm, the exposure must be accompanied by hyperpnea. Ventilations in the range of 40 to 60 L/min have been most successful; such ventilations are beyond the usual oronasal ventilatory switchpoint.

There is no longer any question that oral breathing (especially via mouthpiece) causes exacerbation of SO_2-induced bronchoconstriction. New studies reinforce the concept that the mode of breathing is an important determinant of the intensity of SO_2-induced bronchoconstriction in the following order: oral > oronasal > nasal.

A second exacerbating factor strongly implicated in recent reports is the breathing of dry and/or cold air with SO_2. It has been suggested that the reduced water content and not cold, per se, could be responsible for much of this effect. Airway drying may contribute to the SO_2 effect by decreasing the efficacy of SO_2 scrubbing by the surface liquid of the oral and nasal airway. Drying of airways peripheral to the laryngopharynx may result in decreased surface liquid volume to buffer the effects of SO_2.

The new studies do not provide sufficient additional information to establish whether the intensity of the SO_2-induced bronchoconstriction depends upon the severity of the disease. Across a broad clinical range from "normal" to moderate asthmatic there is clearly a relationship between the presence of asthma and sensitivity to SO_2. Within the asthmatic population, the relationship of SO_2 sensitivity to the qualitative clinical severity of asthma has not been studied systematically. Ethical considerations (i.e., continuation of appropriate medical treatment) prevent the unmedicated exposure of the "severe" asthmatic because of his dependence upon drugs for control of his asthma. True determination of sensitivity requires that the interference with SO_2 response caused by such medication be removed. Because of these mutually exclusive requirements, it is unlikely that the true SO_2 sensitivity of severe asthmatics will be determined. Nevertheless, more severe asthmatics should be studied. Alternative methods to those used with mild asthmatics, not critically dependant on regular medication, will be required. The studies to date have only addressed the "mild to moderate" asthmatic.

Consecutive SO_2 exposures (repeated within 30 min or less) result in a diminished response compared with the initial exposure. It is apparent that this refractory period lasts at least 30 min but that normal reactivity returns within 5 h. The mechanisms and time course of this effect are not clearly established but refractoriness does not appear to be related to an overall decrease in bronchomotor responsiveness.

From the review of studies included in this addendum, it is clear that the magnitude of response (typically bronchoconstriction) induced by any given SO_2 concentration was variable among individual asthmatics. Exposures to SO_2 concentrations of 0.25 ppm or less, which did not induce significant group mean increases in airway resistance also did not cause symptomatic bronchoconstriction in individual asthmatics. On the other hand, exposures to 0.40 ppm SO_2 or greater (combined with moderate to heavy exercise) which induced significant group mean increases in airway resistance,also caused substantial bronchoconstriction in some invididual asthmatics. This bronchoconstriction was associated with wheezing and the perception of respiratory distress. In several instances it was necessary to discontinue the exposure and provide medication. The significance of these observations is that some SO_2-sensitive asthmatics are at risk of experiencing clinically significant (i.e., symptomatic) bronchoconstriction requiring termination of activity and/or medical

intervention when exposed to SO_2 concentrations of 0.40 ppm or greater when this exposure is accompanied by at least moderate activity.

CHAPTER 6. REFERENCES

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